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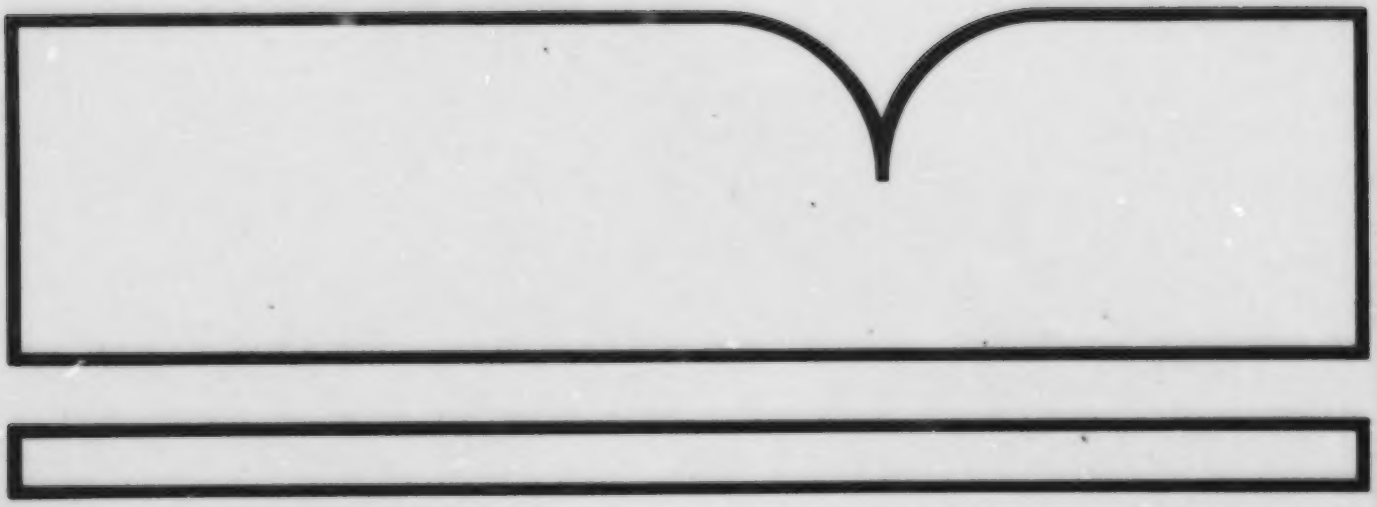

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SOMATOSENSORY EVOKED POTENTIALS

by

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16. ABSTRACT

Somatosensory evoked potentials (SEPs) have been used by neuroscientists for many years. The versatility of the method is attested to be the differing purposes to which it has been applied. Initially, SEPs were used to uncover basic principles of sensory processing. A casual glance at the leterature might suggest that SEPs fell from favor and that over the last decade there has been a renaissance in their use (and the use of evoked potentials in general). More careful scrutiny indicates that use of the method has continued to increase at a steady rate, but that the arenas in which it has been used have shifted from those of basic to those of applied problems. With the advent of more advanced mocroelectrode techniques, SEPs were displaced from the basic neuroscience laboratory to the clinic, where they have been used by psychologists and neurologists. In turn, the apparent utility of the SEP in addressing applied problems has lead to a renewed interest in some of the basic mechanisms underlying the recorded responses. The goal of the present chap ter is threefold. First, to provide a critical summary of the contemporary uses of SEPs; second, to explore the potential utility of SEPs in neurotoxicology; and third, to identify some of the issues which must be addressed in order to perform good neurotoxicological experiments using SEPs.

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I. Introduction

Somatosensory evoked potentials (SEPs) have been used by neuroscientists for many years. The versatility of the method is attested to by the differing purposes to which it has been applied. Initially, SEPs were used to uncover basic principles of sensory processing. A casual glance at the literature might suggest that SEPs fell from favor and that over the last decade there has been a renaissance in their use (and the use of evoked potentials in general). More careful scrutiny indicates that use of the method has continued to increase at a steady rate, but that the arenas in which it has been used have shifted from those of basic to those of applied problems. With the advent of more advanced microelectrode techniques, SEPs were displaced from the basic neuroscience laboratory to the clinic, where they have been used by psychologists and neurologists. In turn, the apparent utility of the SEP in addressing applied problems has lead to a renewed interest in some of the basic mechanisms underlying the recorded responses. The goal of the present chapter is threefold. First, to provide a critical summary of the contemporary uses of SEPs; second, to explore the potential utility of SEPs in neurotoxicology; and third, to identify some of the issues which must be addressed in order to perform good neurotoxicological experiments using SEPs.

Understanding the content of this chapter will be facilitated by a simplified review of the cutaneous somatosensory pathways (proprioceptive pathways will not be discussed). Detailed discussion of the physiology and anatomy of cutaneous sensation may be found in Darian-Smith[1], Mountcastel[2] and Perl.[3] While the somatosensory system contains the longest axons of any sensory system, the basic layout is remarkably simple. First order neurons have their cell bodies in the dorsal root ganglia. In the periphery, the receptors are at the ends of what appear to be long axons, although strictly speaking they are dendrites since the normal flow of activity from them is towards the first order neuron cell body rather than away from it. Action potentials generated at the receptors are transmitted along peripheral nerves, past the cell body, into the spinal cord. It is important to note that for the most part, peripheral nerves do not segregate fibers of different sizes or types. Thus, a given peripheral nerve may contain large and small sensory fibers as well as motor fibers. Once inside the spinal cord, there are two basic somatosensory pathways, the dorsal column pathway and the spinothalamic pathway. At this point the pathway a particular fiber takes does depend upon fiber size, fiber type, and nature of the sensation mediated.

Large (A alpha and A beta) fast (≈100M/sec) fibers bend rostrally upon entering the cord, and ascend in the dorsal columns or spinocervical tract to the medulla. At the medulla these fibers synapse in the dorsal column nuclei. Axons from dorsal column nucleus cells cross the midline and ascend in the medial lemniscus to the thalamus, where they form synapses largely with cells in the lateral portion of the ventrobasal

complex. Axons from cells in the ventrobasal complex ascend to the somatosensory cortex, where they terminate in locations dependent upon the part of the body they represent. This dorsal column system is thought to mediate the most complex aspects of mechanoreception, including tactile discrimination and sensory control of movement.

Small (A delta and C) slow (<30 M/sec) fibers, upon entering the spinal cord, synapse immediately in the dorsal horn, primarily in layer V, but also in layers I, IV and VI. Axons from the second order neurons cross to the other side of the cord, where they ascend in the spinothalamic tracts all the way to the ventrobasal complex of the thalamus. As with the dorsal column system, the third order neurons in the spinothalamic system carry action potentials from the thalamus to the somatosensory cortex, where they too terminate in a topographic fashion related to the sensory field of origin. The spinothalamic system is presumed to mediate such course sensations as pain and temperature. These pathways are summarized in Fig 1.

---

insert Fig 1 about here

Electrical stimulation of a peripheral nerve is likely to activate both the dorsal column and spinothalamic systems, since most peripheral

nerves contain a mixture of axon sizes and types. The resulting evoked potential waveform recorded at the cortical level is therefore an integrated reflection of multiple inputs. SEPs have been recorded from many noncortical levels, including the mixed peripheral nerves, various levels of the spinal cord, brainstem and thalamus. This chapter will focus on the waveforms which may be recorded from the scalp, skull or cortex, although as will be seen, inferences may be made about some subcortical activities from these recordings.

II. The Phenomenology of SEPs

Perhaps more than any other literature on commonly recorded evoked potentials, the SEP literature is characterized by basic differences between laboratories in the morphology of the waveforms reported. The mean and range of latencies of major evoked potential peaks recorded from the scalp of humans following stimulation of the median nerve in seven different groups of subjects are illustrated in Fig 2. This plot does not reflect far-field responses (see below).

Insert Fig 2 about here

In addition to variability between studies in mean peak latencies, there is also variability between studies in the amount of intra study variability. Coefficients of variations were calculated for each peak in the studies used to construct Fig. 2, and the means and ranges of these values are presented in Table 1. The Table illustrates that contrary to conventional wisdom, variability in the latency of late peaks is not much greater than variability in the latency of early peaks. The Table also indicates that not all groups of subjects display all peaks.

Insert Table 1 about here

Between-study variations in SEP waveform morphology are important for several reasons. If a waveform is to be used as a means to detect and characterize dysfunction, one must be capable of comparing types of effects across studies. For example, if one laboratory finds that toxicant A produces a 50% reduction in the amplitude of a positive wave that peaks 20 msec after the stimulus, and another study finds no effect of the closely related toxicant A', but also shows no positive peak in control animals anywhere near 20 msec, very little can be said about the relative effects of A and A' on the somatosensory system. Further, it will always be desireable to link changes in waveform properties with the underlying physiological processes. Since each study will not be able to assess the physiological processes which underlie the waveforms it reports, reliance must be made upon historical determinations. Yet it is not possible to rely upon the results from previous studies if the waveforms have markedly different morphology. Therefore some standardization of waveforms, as appears to have occurred in the visual system 4,5 is desirable.

SEP Peak Nomenclature

Three strategies for labelling EP peaks have been commonly employed. First, peaks may be simply numbered consecutively, I, II, III, etc. Second, peaks may be identified by their polarity and consecutive numbers, such that the first negative peak is N1, the third positive peak is P3, etc. The third strategy is to identify the peak by its polarity and approximate latency, such that if the first negative peak normally occurred between 19 and 21 msec after the stimulus, it would be designated N20. The first strategy has commonly been mixed with the others, such that early far field positive peaks (see below) may be designated I, II, III, but that the first cortically-generated positive peak may be called P1. Comparing waveforms between studies is often difficult because of these different strategies, yet there are occasions when each appears appropriate. For example, when comparing SEPs between species, it makes more sense to compare the properties of the first cortical peaks than to try to keep track of the equivalent latencies for them all. On the other hand, when comparing waveforms recorded from different loci in the same subject, it makes more sense to keep track of the latency than the peak number. For example, if a recording is obtained from the contralateral central area of humans (C4) referred to the midforehead (Fp_z), the first negative peak following median nerve stimulation will be at about 20 msec (N1=N20). However if the recording is made between the neck (e.g. C2) and Fp_z, the negative peak occurring 20 msec after stimulation will be the third negative peak (N3=N20), yet the N20 peak has the same generater in both cases.[6] In this chapter an effort will be made to provide the reader with both types of information. Peaks which are clearly precortical in origin but which can

be recorded from the scalp will be identified with consecutive Roman numerals, unless otherwise stated. Cortically generated peaks will be identified by polarity and peak number. If the authors have used a peak latency designation, this will be included in parentheses.

Once a waveform has achieved some standardization, it is desireable to also achieve an understanding of the generators of the waveform. Such an understanding comes at a cost of great effort, since it entails evaluating (1) the area from which the SEP is maximally recorded (which may be different for different peaks in an SEP); (2) the cortical depth of the active area (if the source is in fact in the cortex); (3) the inputs to the active areas (e.g. are they local, thalamic, commissural, etc.); and (4) whether the peak reflects predominantly excitatory or inhibitory activity.

It is not necessary that a full understanding of SEPs be achieved if the technique is to be used only as a screen. In the simplest screening case it is only necessary to know that waveforms from a treated group are similar to or different from those of a control group. However since EP waveforms do contain information which may allow some characterization of the nature of differences from control, it makes sense to capitalize when possible. Indeed, it will be suggested below that the SEP is most useful in verifying the existence and pinpointing the locus of somatosensory dysfunction, and of questionable value for general screening.

A few published studies have described in detail attempts to determine the active areas responsible for SEPs produced in the cortex. Arezzo et al.[7] report spatio - temporal properties of SEPs evoked in macaques by

electrical stimulation of the contralateral median nerve. Figures 3, 4 and 5 illustrate some of their findings.

Insert Figs 3-5 about here

Fig 3 shows SEPs recorded from 4 epidural loci in the unanesthetized macaque. The surface distribution of the identified peaks is illustrated in Fig 4. If a common underlying circuitry was responsible for the entire waveform, all isopotential maps in Fig 4 should be identical. Clearly they are not all identical. It is evident that owing to unique loci for the different peaks, slight variation in electrode location can increase or decrease the amplitude of selected peaks, independent of others. This finding has important implications for neurotoxicology. Between-subjects experimental designs must take extraordinary care to ensure uniform electrode placement across subjects. Fig 5 makes the point that the sources for the various SEP peaks are cortical and not subcortical, since polarity of the response reverses as an electrode is moved through the cortex.

According to Arezzo et al.[7] P1 (P10) and P2 (P12), the earliest cortically generated SEP components in macaques, arise in Brodmann's area 3, and Brodmann's areas 1 and 2, respectively. Both peaks are resistant to barbiturate anesthesia. The P4 (P20) peak, only present in the alert monkey, is generated in areas 2 and 5. It is noteworthy that

area 5 receives multimodality input, and has been associated with complex processing of somatosensory information, and that the human "equivalent" of this peak (P40) may bear some relationship to cognitive function.[8] The P6 (P40) peak appears to arise from area 7a, while the P8 (P110) peak originates over a wide range of cortical areas, including areas 5 and 7b. There appear to be good correlations between the topography of these peaks recorded from monkeys and those recorded from humans, although absolute latencies are longer in the human case.[7,9]

The Arezzo et al.[7] study represents a major step in our understanding of the various waveform morphologies recorded from the monkey, as well as the topographic location of the generators. Further steps must be taken to understand more fully the microcircuitry within the cortex responsible for locally generated peaks, including identification of the relative roles of EPSPs and IPSPs in different cell layers which generate each peak. The magnitude of the task yet to be performed may be appreciated when considering we have only discussed stimulation of the median nerve. Other commonly stimulated sites are the tibial nerve, the sural nerve, peroneal nerve, sciatic nerve, and trigeminal nerve. While stimulation of each of these sites may produce a different waveform with different topographic distribution, some principles may be emerging. For example, a recent study by Dong and Chudler[10] investigated the origin of SEPs recorded in cats following toothpulp stimulation. The earliest activity of cortical origin was a positive peak which occurred with a latency of about 6 msec,

and like the human monkey cases, had its source in Brodmann's area 3.

Far Field Potentials

To this point, discussion has focussed upon SEP components which reflect activity in the cortex. The last 7 years has witnessed an explosion of interest in the small short latency potentials which precede the cortical SEP waves. These "far-field," or short latency potentials are presumed to reflect activity volume conducted from different subcortical loci and as such may provide a means to monitor with some precision the site of dysfunction in the diseased or otherwise dysfunctional nervous system. Fig 6 contains examples of far-field SEPs (ffSEPs). Note that the peaks are often inflection points which barely disturb the rising slope of the initial cortical peak. In order to detect these tiny peaks reliably and accurately, one must average more responses than with cortical SEPs (usually > 500 responses, as compared to about 100 responses). In addition, greater care must be taken to avoid filtering of the high frequencies which make up the ffSEP components.

Insert Fig 6 about here

While the final word on the sources for each of the ffSEP peaks has certainly not been written, it seems likely that the waves reflect activity of action potentials in tracts, rather than EPSPs and IPSPs[1]. The three positive peaks occurring prior to the initial cortical

response (N1 in humans) have been described as arising from the thalamus (I), thalamocortical afferents (II) and further thalamocortical afferents (III) in rats, cats, monkeys and humans[12,13], or from the posterior columns of the spinal cord (I), posterior column nuclei and medial lemniscus (II) and thalamus and thalamo-cortical radiations (III) in rats.[14] The former interpretation is supported by recordings from shoulder, neck and skull/scalp in the indicated species, while the latter is supported by direct recordings from subcortical loci as well as ability to follow stimuli of varying frequency. A comparison of peak latencies recorded from rats in the above two studies suggests that different waveforms may have been recorded, since the response Wiederholt and Iragui-Madoz[14] report as I occurred at a peak of about 2.01 msec after the stimulus, while the apparently same peak (from inspection of the Figures) in the Allison et al.[13] study had a latency of 4.9 msec. The difference is probably not accounted for by the fact that Allison et al.[13] used a stimulus intensity just sufficient to produce a finger movement while Wiederholt and Iragui-Madoz[14] used an intensity sufficient to produce a maximal amplitude P1, since the P1 latencies reported in the two studies were quite similar, 7.5 and 7.0 msec, respectively. If stimulus intensity accoun - ted for the differences, then the cortical response should have been more delayed in the Allison et al.[13] study than the 0.5 msec indicated. Differences in recording electrode placement may account for the different morphologies.

Arezzo et al.[15] have pointed out some of the difficulties in identifying sources of ffSEP peaks. First, since by definition far field

potentials are widely recorded, selection of an "indifferent" reference electrode is problematic. The optimal location for the reference electrode must be based not only on distance from the source, but also on a knowledge of the presumed geometry of the source. In particular, Arezzo et al.[15] recommend that for stimulation of the median nerve an appropriate reference site is the contralateral wrist, which happens to lie in a direction perpendicular to the rostro-caudal axis of maximum field potentials produced by the stimulus.

Second, Arezzo et al.[15] caution against inferring sources based solely on appropriate latencies of potentials recorded from a particular candidate locus. The candidate locus may have a geometry which makes generation of far field potentials unlikely. For example, the ventrobasal complex of the thalamus and the dorsal column nuclei appear to have a "closed field" geometry, which would minimize spread of postsynaptic potentials. The potentials generated at this putative source may merely overlap in time with potentials generated more caudally. Thus, unequivocal identification of a source requires stepwise tracing of the potential from its maximum to the location from which recordings are normally made. From these considerations it is evident that further analysis of the interpretation of Wiederholt and Iragui-Madoz[14] and Allison et al.[13] may be in order. Recent intracranial recordings from humans have made a compelling case that the three most prominent far-field waves recorded from scalp loci: I (P9), II (P11), and III (P14), derive from peripheral nerve, cervical dorsal column, and medial lemniscus, respectively.[16,17]

The brainstem auditory evoked response (BAER) was the first far field potential to achieve wide acceptance as a clinical measure.[18] An appealing characteristic of the BAER is that subtracting the latency to the first peak from the latency to the last peak provides what has been called central conduction time. Central conduction time is not affected by alterations in the periphery, since these would be constant at the first and last peak of the response. Therefore the measure provides an index of the integrity of function within the brainstem. A similar measure has been developed and is becoming popular in the somatosensory system.

In the somatosensory system the most common technique for determining central conduction time has been to obtain separate recordings from the neck and scalp following stimulation of either the median or peroneal nerve.[6,19,20] When the human median nerve is stimulated, the measure of central conduction time is given by N20-N14, where N20 is presumed to reflect the first cortically generated peak and N14 is presumed to arise from the dorsal columns in the cervical cord.

Species Comparisons

As with any endpoint under consideration for use in assessing toxicity, it is important to evaluate generality across species. One of the major advantages of sensory evoked potentials (not just SEPs) is that they may be recorded noninvasively from humans, thereby raising the prospect of a very direct extrapolation from laboratory animal to human. In order to capitalize upon this prospect, one must establish the analogies and homologies between waveforms recorded from humans and

various species of laboratory animal. Having done so, it may be possible to use species like the rat for screening and early characterization purposes, while reserving more expensive species like monkeys for selected cases.

In drawing comparisons between waveforms recorded from different species, three constraints should be considered. First, and perhaps most obvious, is that absolute latency is not a useful cross-species comparison variable. Latency is directly related to length of the pathway, and inversely related to diameter of the stimulated fibers. While an approximate length of the pathway may be determined noninvasively with a tape measure, diameter of the stimulated fibers may not. Small animals like the rat have shorter pathways than humans, thereby decreasing SEP latencies. However the rat also has small diameter fibers, thereby increasing SEP latencies. Consequently initial comparisons between species are most sensibly made on a peak number rather than a peak latency basis (e.g. first peak, second peak, etc.).

Second, one cannot assume a priori that the synaptic inputs to homologous brain regions are the same. In a hypothetical case, the first positive peak recorded from one brain region in the monkey might reflect locally generated activity, while the homologous peak in a rat may reflect volume conducted activity from a nearby cortical area. The peaks are homologous but not analogous. In view of this possibility, direct comparisons between species are inappropriate until some evidence exists that the comparison peaks have common determinants (are analogous). If such comparisons are to be made despite their inappropriateness, peak number should be used for the description. The underlying principle is that in the absence of analogy, homology is better than choas.

The validity of cross-species ffSEP comparisons has been addressed by Allison and Hume[12] and Allison et al.[13]. Allison and Hume[12] performed surface and depth recordings in monkeys and cats, comparing their findings to surface recordings from monkeys, cats, rats and humans. All stimuli were applied to the median nerve at the wrist, with intensity just sufficient to elicit a twitch in the first digit. For recordings intended to reflect cortical activity, the reference was placed either in the frontal bone or in the overlying scalp. Active electrodes were placed over contralateral parietal areas, although it is not clear what criteria were used for this placement in cats and rats.

Initial cortically generated activity was a positive wave in rats and cats, but a negative wave in humans in monkeys. Nevertheless, depth recordings provided evidence that these reflected similar generators. The mean latencies of this first cortical peak were 19.2, 12.0, 11.3 and 7.5 msec for humans, monkeys, cats and rats, respectively.[13] The between species surface polarity difference is presumed to reflect the presence of a complex gyral pattern in primates. Figure 7 shows schematically the relative latencies of peaks between species, and Table 2 shows the actual latencies recorded.

Insert Fig 7 about here

Insert Table 2 here

As suggested above, the presence and nature of gyri near the recording electrode can produce drastic between-species alterations in surface topography of recorded potentials. An example of how such changes might occur may be seen in Fig 8.

Insert Fig 8 about here

It would appear that matters would be simplest in the lissencephalic brains of such animals as rats. While this may be true theoretically, the absence of gyri presents special problems of its own. In primates and carnivores the boundaries of many cytoarchitectonic fields may be approximated or even defined by the gyral pattern. For example, the primary somatosensory cortex, generally recognized as Brodmann's area 3, is considered to be on the postcentral gyrus of humans and postcentral gyrus of macaques. Raccoons appears to have an individual sensory gyrus for each finger and volar area of the paw.[21] In rats there are virtually no surface landmarks to be used, although some have attempted to relate vascular patterns to underlying brain area.[22] A recent effort, which mapped the secondary somatosensory area of the rat forepaw, attempted to use skull landmark.[23] The authors reported that while the target

area was about 0.5 mm in diameter, its location with respect to skull landmarks varied from rat to rat by as much as several mm. What these findings suggest is that while one is less likely to be fooled by surface topography-related polarity inversions in the rat, one is more likely to have difficulty reproducing from one rat to the next the optimal recording site. Or, put differently, a recording site determined a priori according to skull surface landmarks, as is likely to be the case in chronic studies,[24,25] is likely to produce data with significant between animal variability.

These caveats not withstanding, some information regarding the presumed location of somatosensory cortex in rats will be provided. Figures 9 and 10 are maps which reflect the cortical distribution of single units responsive to stimulation of different regions of the body in anesthetized rats.[26,27]

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insert Fig 9 and Fig 10 about here

It is unfortunate that neither map shows a representation of the tail, since the tail contains the most accessible nerves for stimulation in rodents.[24,25,28,29] It is also evident from the figures that the head region is afforded by far the most expansive cortical representation. Indeed, Welker[22] estimated that while the entire trunk and tail of the rat was represented by about 7% of the primary somatosensory cortex (SmI), the

vibrissae, head and neck region was represented by over 66% of SmI. Investigators interested in using SEPs to study the rat somatosensory system could profitably attend to this anatomical convenience, but none have yet done so.

Only one paper was found which attempted to plot in a systematic way rat SEP amplitude as a function of skull location.[30] In this case the primary interest was in comparing the distribution of what is probably a P2 response as a function of type of stimulus to the hindleg. However the absence of any comparative identification of this peak with other peaks in the literature, despite the fact that it is shown to reverse polarity in the cortex, diminishes its contribution.

There have been sufficiently few rat SEP papers that it is possible to display a good percentage of them in Fig 11. This figure shows waveforms redrawn from several studies on rats. From this figure it may be seen that significant cortical activity follows the initial P1 response in most cases, but only rarely did the papers attend to these later peaks. Table 3 provides information on the recording and stimulating loci for the waveforms depicted in Fig 11.

Insert fig 11 about here

Insert table 3 about here

While the difficulties associated with recording from the lissencephalic brains of animals with only minimal cortical representation of limbs may account in part for the relatively meagre output of rat SEP papers, neurotoxicologists should be quick to recognize the value in using this economical species. The aforementioned concerns are much less compelling in the case of ffSEPs, since they are widely distributed across the skull, and it may be that this waveform will be of significant use to neurotoxicologists.

Development of the SEP

Charting the developmental course by which an evoked potential reaches its adult configuration should provide clues to the stage of development of the underlying neuronal processes. Alterations in the development of a waveform produced by a toxicant may in turn be used to infer abnormal development of the nervous system. Detailed and contemporary studies of the development of SEPs in nonhuman species are rare. However several careful studies in humans, describing developmental changes at both ends of the age spectrum, provide useful information.

In the young of many species, including newborn kitten,[31] premature sheep,[32] rabbit,[33] and premature baboon,[34] the first poststimulus (median nerve) sign of cortical activity is a surface negative wave. It has been presumed that this wave corresponds to the N1(N22) wave in humans.[35] In humans the amplitude of N1 does not change between 3 months and young adulthood, but its duration gradually decreases during this time.[35] In adult members of nonhuman species, with the exception of macaques, the first poststimulus sign of activity recorded from the cortex is positive, not

negative. It has been presumed that differential maturation of apical and basal dendrites converts the negative wave into a positive wave in older animals,[35] and that therefore N1 in adult monkeys and humans is functionally equivalent to P1 in other species.[13] In fact, it is not known that the negative wave which appears around birth in many species does correspond to N1 in humans, nor is it known that it is this same wave which changes polarity to become P1 with progressive development or whether the same sequence of events pertains to all these species. For example, stimulation of the tibial nerve produces a surface negative wave in newborn rats,[36] and while several studies have shown that this surface negative wave is retained, it appears that a surface positive wave may emerge at an earlier poststimulus time during the third postnatal week.[37,38]

The apparent corespondence between the human and monkey N1 on the one hand, and, for example, the cat P1 on the other, makes determination of the origin of the transient N1 in nonprimates of some interest.[12] In aged humans the amplitude of N1 increases, a phenomenon which is accompanied by but not highly correlated with an increased duration of the wave.[39] No studies of SEPs in aged nonhuman species were found, but it would be of interest to learn whether an early negative wave reappears in aged nonhuman species, or whether any other waves change with age in a manner that parallels the changes in the human N1.

A simple analysis of the onset latency of the N1 peak in humans reveals strikingly little change across the first 8 years of life. However latency is subject to misinterpretation in developmental SEP studies. Pathways become longer until adulthood, thereby producing

decreases in latency. In order to make a rough correction for growth, the latency has been divided by the body size, to produce a msec/meter value. Note that this body size/factor is constant for an individual regardless of which nerve is stimulated. The value obtained should not be confused with the reciprocal of conduction velocity, in which the unit of length is specific to the nerve under test. When plotted this way (see Fig 12), a power function indicates the development of the system.[39] This trend reverses in aged humans, such that N1 latency becomes gradually longer between ages 18 and 95.[40] At least some of this increase is evidently due to slowed central conduction time in older subjects.[41]

Insert Fig 12 about here

The first positive peak of cortical origin in humans, P1, develops its adult latency at about the same rate as N1,[40,35] but increases from early adulthood to old age more rapidly than does N1, thereby suggesting (1) separate generators; and (2) more rapid aging of one generator than another.[40,41] In contrast to N1, P1 appears to grow in amplitude throughout life.[35,39] This differential shift in peaks with age may be responsible for the higher incidence of the "W" waveform (as described by Giblin[45]) in elderly than young adults.[39]

Gender Differences in SEPs

It is a common observation in the evoked potential literature that there are significant gender differences,[42] and it is therefore not surprising to find such differences with SEPs. As with visual evoked

potentials, SEPs of human females are greater in amplitude than those of males.[43] Latency differences between genders have also been found, with males tending to have somewhat longer latencies. Evidently only part of these differences may be attributed to body size.[40,43]

The preceding sections have described the phenomenology of SEPs, focussing upon where they come from and what they look like. An underlying assumption is that analysis of SEPs may tell us something about the integrity of somatic sensation and the somatosensory system on one hand, and the integrity of brain function in a more general sense on the other. In the following section some of the interpretations which have been applied to alterations in SEPs will be discussed.

Interpretation of SEPs

Relationship of SEPs to Perception

While there is little need to doubt a relationship between SEPs and the perception of somatic sensation, there have been only a few attempts to explore the nature of the relationship. Soininen and Jarvilehto[44] have demonstrated in humans that reliable SEPs could be recorded at the detection threshold for tactile stimulation, but not below. The authors described a series of positive and negative peaks following threshold stimulation, but the waveform reported is not easily compared to other published waveforms since most other studies have used stimuli so great that latencies would be considerably shorter and amplitudes considerably larger. Further, use of natural (mechanical) stimulation instead of the more traditional electrical stimulation would not be expected to activate the large, fast conducting muscle and joint afferents mediat-

neuronal activity present in many SEP studies was not present in the Soininen and Jarvilehot[44] study. These unusual characteristics of the study permitted some remarkable findings. The recorded waveforms were not simply a reflection of stimulus amplitude, since on some trials a stimulus with a particular intensity was detected while on other trials a stimulus of the same intensity was not detected. When the detected trials were averaged, an SEP was present, but when the undetected trials with the same intensity stimulus were averaged, an SEP was not observed. In other words presence of the waveform was associated more with sensation than with the physical properties of the stimulus.

SEPs recorded following electrical stimulation of a mixed nerve such as the median nerve may largely reflect the integrity of the sense of joint position, since this sense is carried by the largest and fastest fibers. The Soininen and Jarvilehto[44] study demonstrates that under appropriate conditions, SEP amplitude reflects light tactile sensation. It is difficult to test the integrity of the pain and temperature senses in mixed nerves since fibers which carry pain and temperature information have high thresholds and are slowly conducting. Indeed, clinical studies have indicated that humans with inability to experience pain and temperature due to spinal cord lesions may have normal SEPs.[45]

Nevertheless there are SEP paradigms which may be useful for assessment of pain as well. A delta and C fibers are presumed to mediate the sensation of pain. Since the tooth pulp contains primarily A delta and C fibers,[46] electrical stimulation of the tooth pulp has been used as a model system for studies of pain. In this context, SEPs evoked following tooth pulp stimulation have been investigated as objective measures

of pain. The SEP recorded from the vertex following tooth pulp stimulation is composed of 3 negative peaks and 2 positive peaks. The latencies of these peaks vary with the study, but N1 normally appears between 60 and 80 msec, P1 between 80 and 140 msec, N2 between 175 and 260 msec, and P2 between 260 and 400 msec.[47,48] While it is not clear whether there is a relationship between the presence and absence of pain reports and the presence and absence of SEPs at perithreshold levels of stimulation, it has been demonstrated that there is a good linear correlation between SEP amplitude and magnitude of the reported painful sensation.[47,48] In these studies amplitude of the later peaks (N2P2 and P2N3) correlated more highly than did amplitude of the early peaks with pain magnitude. Administration of a placebo reduces both the N2P2 amplitude and the reported magnitude of pain, implying that sensation is more potent than stimulus magnitude as a determinant of SEP amplitude Crucco.[49]

From the above studies and others[50] it might appear that amplitude of SEPs evoked by electrical stimulation would correlate with proprioceptive sensation. While this is a difficult assumption to test, some data suggest that it is not entirely accurate. Schiff et al.[51] have recorded SEPs from a population of patients with focal disease of the spinal cord which included some with proprioceptive deficit. While it was true that most of the patients with a proprioceptive deficit had abnormal SEPs, it was also true that many patients without disordered proprioception had disordered SEPs. Only latencies were evaluated, and a direct test of the hypothesis is therefore not possible, but it is noteworthy that one patient had apparently normal proprioception but an absent scalp response to peroneal nerve stimulation.

The underlying principle of interpretation to be learned from these studies is that amplitude of the SEP may be correlated with magnitude of sensation, as long as care is taken to study only the sensation mediated by the largest and fastest fibers likely to be activated by the stimulus. It is also important to note the possibility that while such relationships may exist in the normal brain, the correlations may break down under conditions of disease or neurotoxic insult.

SEP Changes in Neurological Disorders

Various investigators have reported SEP changes in patients with neurological disorders ranging from focal peripheral lesions to diffuse and global cerebral dysfunction. While it may not be reasonable to expect wholesale parallels between findings reported in the neurological clinic and those obtained in the neurotoxicology laboratory, awareness of the kinds of abnormalities observed in patients with known or presumed neurological disease may aid neurotoxicologists to interpret their own findings.

As would be expected, peripheral nerve lesions produce abnormalities in SEPs recorded from the scalp. Typically, SEP amplitudes are greatly diminished and latencies are increased, both in rough proportion to the extent of damage. Occasionally these changes precede clinically detectable sensory dysfunction. When a focal disorder such as carpal tunnel syndrome is present, the waveform morphology is relatively normal, but shifted in latency. Other peripheral nerve disorders may produce gross waveform distortion Giblin.[45]

Spinal cord lesions produce effects upon SEPs which seem to be partially dependent upon location of the lesion. Lesions in humans involving the dorsal column system may abolish SEPs, while anterolateral

tractotomy may leave them unaffected.[45] Demyelinating disease produces increased latencies, even in some cases when no clinical deficit in joint position sense has been detected.[52]

It should be noted that in most cases in which electrical stimulation has been used, a stimulus intensity is chosen which is either near threshold intensity or at a small multiple (usually 2) of the threshold intensity required to produce a motor response. Use of these stimulus intensities may account for the failure to detect from SEPs any alterations in pathways carrying higher threshold pain and temperature information. Powers et al.[53] used high intensity (20 times the motor threshold) stimulation of the posterior tibial nerve in a series of cats with nine different combinations of unilateral spinal cord lesions. The cats were anesthetized with a ketamine xylazine mixture. Immediately after motor threshold was determined, they were paralyzed to avoid the recording difficulties associated with movement and muscle artifacts.

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insert Fig 13 about here

Fig 13 illustrates the altered waveform morphology produced by higher intensity stimulation. Several late negative peaks are evident in the records following high intensity stimulation which are not present in the records following threshold stimulation. Lesions in the dorsal columns resulted in severe attenuation of amplitudes of early (P1N2) and late (N4) peaks measured from the side of the brain ipsilateral to the lesion. Lesions of the ventrolateral tracts resulted in moderate attenuation of early and late ipsilateral peaks and severe attenuation of late contralateral peaks. Lesions of the dorsal

spinocerebellar tracts resulted in severe attenuation of the early ipsilateral peaks. One may conclude from this study that with sufficiently intense stimulation an accurate picture of the integrity of the major ascending spinal cord tracts may be obtained from SEPs. High intensity stimulation is not practical under most circumstances because it is painful and may produce large movement artifacts, but it may be useful in neurosurgery because the subjects are anesthetized and often paralyzed as well.

When damage occurs at subcortical levels, and conventional stimulation and recording configurations are employed, the preceding summary indicates that the typical finding is either an increased latency and/or decreased amplitude of N1 (or P1), the first cortical peak. Other later peaks are generally shifted and decreased as well.[54]

When the damage is cortical, more complex patterns of change are observed, and in some cases the pattern of change may aid in localization of the lesion. In a series of 30 patients, Stohr et al.[55] found that SEP abnormalities could be divided into 4 types, each of which was associated with a different type of lesion. The type 1 SEP, characterized by abnormalities at all points beyond the last far-field response recorded with a frontal reference (a positive peak at 15 msec), reflected lesions of the thalamus, internal capsule and centrum semiovale. Severe attenuation of N1 (N20) and subsequent components defined a type 2 SEP, and these were associated with lesions of the postcentral gyrus. When N1 was spared but later waves lost, damage was presumed to be in parietal association areas and the response was designated a type 3 SEP. A type 4 SEP was rare. In this case, damage was in area 39, and only peaks N3 (N55) and beyond were affected.

These findings generally parallel what would be expected based upon the report of Arezzo et al.[7] in monkeys.

Mauguiere et al.[56] correlated median nerve evoked SEPs with a detailed clinical examination and computerized tomographic scanning in a series of 22 patients with single circumscribed hemisphere lesions outside the basal ganglia. Responses were compared to those obtained from the unaffected hemisphere. While the onset latency of N1 (N20) recorded from scalp overlying parietal cortex was normal in these cases, the peak latency was delayed about 5% (1.1msec). Small lesions of the postcentral gyrus which preserved tactile and deep sensation were sufficient to produce astereognosis and to reduce or eliminate N1 and P1. Similarly, Obeso et al.[57] demonstrated that focal lesions restricted to primary somatosensory cortex produced increased latency of N1 (N22) recorded from the affected side in 90% of cases, and decreased N1 amplitude almost as often (81%). Changes detected in N2 (N39) and N3 (N70) were of similar character, but were observed in fewer cases.

It might seem that increased latency and decreased amplitude are the only possible outcomes of EP studies in the presence of neurological damage. However enhanced SEP amplitudes have been reported to follow several types of dysfunction. For example, Mauguiere et al.[56] observed that a response (P22-N30) which can be recorded from precentral gyrus (motor cortex) following median nerve stimulation was actually enhanced when parietal lesions were present. Obeso et al.[47] found that focal cortical damage remote from the recording site tended to produce increased amplitudes. For example, in patients with a unilateral lesion involving primary sensorimotor cortex, SEP N1 (N22) amplitudes recorded from the intact (contralateral) hemisphere were larger than those in

control subjects 33% of the time, and smaller in less than 10% of the cases. Further, when the lesion was ipsilateral to the recording site but distant from it (i.e. in frontal, temporal or occipital lobes), SEP N1 (N22) amplitudes were increased in 80% of cases, and decreased in the other 20%. Surprisingly, N1 (N22) and N2 (N39) were more often affected than N3 (N70). Intuitively one might suppose that distant damage would have a more potent influence on late rather than early peaks.

Other studies have demonstrated selective enhancement of later SEP components. For example, some patients with Down's Syndrome have large late SEP components.[58] In a study involving Macaca speciosa monkeys, Watson et al.[59] demonstrated that a unilateral lesion in the frontal arcuate cortex had no effect upon N1 (N13), but increased latency and amplitude of P3 (P100). This same lesion produced the unilateral neglect phenomenon. While these findings are of interest, their interpretation must be tempered with the knowledge that only three monkeys were involved, and there may have been pre-lesion differences between the side of the brain on on which lesions were ultimately made and the contralateral side, which was used as the control.

In cats, kindling of the cortex results in enhanced amplitudes of N2P3N3 following stimulation of the forepaw.[60] These enhanced SEPs may have determinants which are similar to those of the giant SEPs observed in humans with certain types of epilepsy and cortical myoclonus.[61] In the latter cases, N1 is usually not changed, but N2 is grossly enlarged. While these giant potentials are evidently not related directly to movement, they may reflect either hypersynchrony in cortical neurons, or an abnormally large input from slower conducting neurons.[62] al.[62]. Similarly Takahashi and

Straschill[63] report that an epileptic focus generated in rats by topical application of penicillin alters SEPs. Following forepaw stimulation, P1 (P7) and N1 (N9) amplitudes were unchanged, but P2 (P13) and N2 (N22) amplitudes were grossly enhanced.

There appear to be a number of reasons why an SEP could be abnormally large. From the preceding it is tempting to conclude that either distant or diffuse cortical damage is likely to increase the amplitude of SEPs. While this conclusion may have some validity, several studies indicate that its generality is limited. Huntington's disease has been associated with increased latency of N1 and depressed amplitudes in later SEP peaks evoked by median nerve stimulation in one study of 21 patients.[64] In another study, 32 patients with Huntington's disease were compared to 30 controls and 41 individuals at risk for Huntington's disease. In this study, latencies were not increased, but amplitudes of N1 and P1 were decreased following both median and tibial nerve stimulation.[65] While procedural differences probably account for the differences between the two studies, it is noteworthy that in both cases amplitudes were decreased.

To summarize, changes in SEPs recorded from subjects with known neurological disorders have provided added clues to aid interpretation of SEPs altered by other means. Damage which is in the subcortical somatosensory pathway tends to increase latency and decrease amplitude of far field and near field SEPs recorded from the scalp. However, without proper stimulating conditions, damage to slowly conducting pathways may be missed. Cortical damage may increase or decrease amplitude of SEP peaks generated in the cortex, depending upon the locus and nature of damage.

Increased amplitudes may reflect distant/diffuse damage, but all distant/diffuse damage need not be reflected in increased amplitudes.

Uses of SEPs

Diagnosis and surgical monitoring

Because of variability in the SEPs recorded from normal subjects, it may never be possible to utilize a particular type of SEP abnormality in and of itself as diagnostic of a particular neurological disease. On the other hand, SEPs can and have been useful diagnostic aids for differentiating between disease states. Neurologists have looked to EPs for aid in diagnosis of multiple sclerosis (MS). While most studies which have compared the relative value of different EP techniques in recognizing MS have concluded that visual evoked potentials are most useful, it is commonly conceded that SEPs (and brainstem auditory evoked potentials) are valuable adjuncts.[66,67,68,69] It has been noted that under conditions of fever or experimental hyperthermia, differences between MS and control patients are enhanced. While increased temperature speeds conduction in the normal nervous system, it has the opposite effect upon those with definite MS.[70,71] SEPs are also altered (increased latency) in cases of amyotrophic lateral sclerosis[72] although these patients have not been evaluated under conditions of hyperthermia.

It is known that with advanced age, SEP latencies and amplitudes increase. When these normal aging changes are taken into account there are no differences between normal subjects and patients with senile dementia of the Alzheimer type. On the other hand, patients with multi-infarct dementia have increased N1 (N20) latency, increased

central conduction time and decreased amplitude compared to Alzheimer patients. Therefore SEPs may aid in discriminating these populations.[73]

In comatose patients there is an increased central conduction time, and occasional disintegration of SEP waves.[74] Recovery of SEP peaks appears to correlate well with recovery of the patient.[75,76,77] Similarly, Goff et al.[78] found that cases of Reye's syndrome, which usualy is accompanied by cerebral edema, are generally associated with marked depression of all SEP components. Recovery of early components was associated with survival, and recovery of components normally occurring with latencies greater than 100 msec tended to predict that there would be no lasting neuropsychological deficit.

Use of SEPs for continuous monitoring of the integrity of somatosensory pathways has become a routine procedure.[79,80,81] In one recently described application,[82] SEPs were used to determine in a direct way the advisability of a particular surgical procedure for each patient. Evaluating the integrity of SEPs during carotid endartectomy allowed the surgeon to decide whether collateral circulation was adeauate, and thereby determine which patients could endure the procedure without a temporary bypass shunt to prevent ischemic brain damage during surgery.

Pharmacology

Anesthesia is at once the most common and heavy handed pharmacological manipulation performed in conjunction with SEP studies. In general these studies indicate that SEP peak sensitivity to anesthesia is correlated with peak latency.[83] Allison and Hume[12] have shown that in cats, rats and monkeys, terminal pentobarbital anesthesia results in retrogressive loss of SEP peaks, from the latest (cortical) to the earliest

(far field). In a human study in which specific peaks were not identified, it was indicated that ulnar nerve SEP alterations depended upon the anesthetic used.[84] In particular, 80% nitrous oxide severely attenuated all late SEP peaks, as did 2% diethyl ether. The entire cortically generated SEP was obliterated by 4% diethyl ether. By contrast Ethrane, a halogenated ether, produced marked increases in SEP amplitude at high concentrations (3%). Pathak et al.[85] report that fentanyl anesthesia (in the presence of 60% Nitrous oxide, secobarbital and atropine) increased all peak latencies, depressed N1P2 and increased P2N2 amplitude of tibial nerve evoked SEPs. Ganes and Lundar[86] recorded SEPs in already comatose patients administered thiopentone, and showed that central conduction time was not altered by the anesthetic, but that all peaks beyond N1(N20) were missing.

Angel et al.[87] used forepaw stimulation SEPs in rats to study the interaction between anesthetic (urethane) requirements and changes in atmospheric pressure. In this case, SEP changes were correlated with changes in the behavioral response to tail shock. Increasing atmospheric pressure produced a linear increase in the anesthetic dose required to maintain a fixed size behavioral response to tail shock. Similarly, increasing atmospheric pressure produced a linear increase in N1 amplitude. When atmospheric pressure was kept constant and urethane dose was increased, N1 amplitude decreased in a fashion which was nearly linear with log dose. From this study one may conclude that monitoring the amplitude of N1 in rats provided a useful measure of depth of anesthesia.

In many studies, the influence of anesthetics on SEPs is intimately tied to the influence of anesthetics on body temperature. Altered body temperature produces altered evoked potentials, and may interact with anesthesia

to produce unique alterations in EP characteristics.[88,89] It is difficult to perform studies in which body temperature is systematically manipulated in the absence of anesthesia. Several studies have recorded SEPs from humans with body temperatures raised either artificially[71] or by fever of extracerebral origin.[70] In both cases, a slight increase in peripheral conduction velocity was reported in the absence of any changes in central conduction time. No changes in amplitude were reported. The temperature range over which these studies were performed (1-2°C elevation) and the absence of information regarding the relationship between brain temperature and body temperature under these conditions limit their generality.

In human studies in which hypothermia was achieved while the subject was anesthetized with fentanyl and nitrous oxide, peak latencies increased in a manner which was inversely proportional to temperature. Later peaks were affected more than early peaks.[82,90] Amplitude of cortically generated peaks following median nerve stimulation decreased with progressive hyp - othermia, but amplitude of one peripherally generated peak (N14), presumed to reflect activity in the dorsal columns, increased by 50% between 33 and 26°C Markand et al.[82]. In cats anesthetized with pentobarbital, hyperthermia - resulted in decreased latency and increased amplitude as temperature rose to about 41°C. Beyond this point, latencies increased and amplitudes decreased.[92]

The results of Budnick et al.[92] in rats anesthetized with sodium pentobarbital essentially parallel those of Markand et al.[82] in humans. The later the normal latency of a peak, the more it was influenced by hypothermia. In general, amplitudes declined with progressive hypothermia, with the exception of component I of the ffSEP, which probably reflects dorsal column activity and which increased in amplitude between 37° and 24°C. These results are quite different from those recorded from the visual system of anesthetized rats,

where combined hypothermia and anesthesia produce an increase in N1 amplitude (the first cortically generated peak), in addition to an increase in all peak latencies.[88,89]

While a number of studies have investigated the role of various neurotransmitters in the functioning of somatosensory cortical neurons,[93] there are relatively few which address the impact of specific transmitter manipulations upon SEPs. One of the most compelling demonstrated that SEPs of cats produced by forepaw stimulation were sensitive to minute quantities of topically applied GABA.[94] Under normal conditions, stimulation produced a fore paw SEP in primary somatosensory cortex of anesthetized cats which was characterized by a P1 (P11) and N1 (N20) wave. Application of 10mg GABA completely abolished N1, suggesting an important role for this inhibitory transmitter in modulating N1 amplitude. Curiously, this effect of GABA could not be blocked by either picrotoxin or bicuculline.

Neurotoxicology

SEPs have been used occasionally but not extensively to detect and characterize neurotoxicity. It has been argued that toxicologists might use EPs for detection of diffuse CNS dysfunction as well as dysfunction specific to the sensory system under test.[5] The previously described studies which reported enhanced amplitude of SEP peaks in cases where damage was not in the primary somatosensory system support this point.[57] For screening purposes SEPs offer two theoretical advantages over other sensory EPs. Transmission from the periphery to the cortex requires activity in such long tracts that extensive opportunity is provided (a) for toxicants to produce dysfunction; and (b) if the dysfunction is diffuse, for it to be exaggerated or multiplied as successive long segments of the pathway are traversed. To date no data support these theoretical advantages.

Rebert[95] has made a case for inclusion of SEPs in a multisensory EP battery for detection and characterization of neurotoxicity. In these studies, rats with chronically implanted skull electrodes for recording SEPs were placed in a tubular restraining device and studied unanesthetized. Stimuli were delivered to the tip of the tail, presumably activating the ventral caudal nerve. However to date no publications have demonstrated that this preparation detects diffuse CNS dysfunction following exposure of adults to toxicants more effectively than EPs in other sensory systems or from simply recording the action potential from the caudal nerve.[96]

Several investigators have used SEPs to study the influence of perinatal exposure to potentially toxic substances upon the normal development of the somatosensory system. Salas and Schapior[37] administered either cortisol or thyroxin to rats on postnatal days 1, 2 and 3, and recorded EPs to somatosensory (sciatic), visual and auditory stimuli on postnatal days 6, 9, 12, 15, 18 and 150. The recordings were made under anesthesia, with the skull exposed. A curious bipolar montage, with two surface electrodes separated by 2-3 mm, makes interpretation of the waveforms difficult. However the authors reported that thyroxin-treated rats had an accelerated course of SEP development, while cortisol treated rats had a retarded course of development. The effects observed were even more prominent in the visual system than in the somatosensory system. The small numbers of rats and the apparent unavailability of a signal averager further hinder evaluation of this study, but the results are provocative since they suggest long term modulation of sensory development by early hormonal processes.[97] Similar studies have indicated that

malnutrition also retards the development of the rat SEP,[98] although effects upon secondary responses were even greater than on the primary response to sciatic stimulation.

Laurie and Boyes[38] recorded SEPs and VEPs in rats following neonatal exposure to diesel exhaust. While little consideration has been given by others to the potential influence of diesel exhaust on the nervous system, Laurie and Boyes[38] reported that SEPs recorded following tibial nerve stimulation were abnormal in the treated animals. Latencies of all peaks were prolonged on about postnatal day 14, and the recoverability of P2 amplitude in a paired stimulation paradigm was impaired on the same day. Changes similar to these were found in the visual system, where one peak exhibited a treatment induced increase in latency. In this case it is difficult to conclude that the somatosensory system was uniquely sensitive, but it may have been slightly more sensitive than the visual system.

It is well known that exposure to lead can slow conduction velocity in peripheral nerves.[99] It has also been reported that lead toxicity is detected by SEPs more readily than by conduction velocity.[100] The latter finding might reflect greater sensitivity of sensory fibers activated during SEP tests than mixed sensory and motor fibers activated during peripheral conduction tests, but the nature of the lead-induced change suggests that this is not the case. Seppalainen[100] reported an 80% increase in the amplitude of the N1-P1 (N18-P22) peak evoked by median nerve stimulation and recorded from rolandic cortex of workers with occupational history of exposure to lead. This finding is illustrated in Fig 14. As noted previously, increased amplitudes are often associated with cortical damage distant from the recording site. Since only 6 subjects were involved

in the high level exposure group, caution is advised in generalizing from these data. Further, the absence of data comparing the effects of lead upon SEPs to the effects of lead on other sensory systems makes evaluation of the sensitivity of the method and the specificity of the effect difficult. When exposure to lead occurs during the perinatal period, rats have definite visual system dysfunction.[101]

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insert Fig 14 about here

SEPs appear to have been most useful to toxicologists when there were a priori reasons to suspect involvement of the somatosensory system. In such cases, recording SEPs can be used to (1) verify involvement of the system; (2) point to the locus of involvement within the system; and (3) trace in vivo the time course of involvement of different structures within the system. For example, Howell et al.[24] suspected involvement of the somatosensory system in rats treated with trimethyltin (TMT). TMT-treated Long-Evans hooded rats engaged in a pattern of self-mutilation of the tail which suggested deafferentation. A hot plate test for behavioral reactivity to thermal pain also suggested somatosensory dysfunction, since TMT-treated rats took longer than controls to exhibit signs of discomfort. Evaluation of threshold and conduction velocity in the dorsal caudal tail nerve revealed no peripheral dysfunction, but SEPs recorded from the skull following tail nerve stimulation had longer latencies and smaller amplitudes in TMT-treated rats than in controls. The SEP technique thereby verified the existence of dysfunction in the somatosensory system, and repeated recordings demonstrated the progressive nature of dysfunction.

While the suggestion was made that the findings indicated central and not peripheral dysfunction, the absence of alterations in nerve conduction velocity may have reflected a blurring of effect due to the mix of sensory and motor fibers involved in the conduction velocity measurement.

Leitch and Hallenbeck[102] used SEPs to monitor the dysfunction produced by spinal cord decompression sickness in dogs. SEP amplitude changes appeared to correlate with changes in cerebral blood flow, although the small number of dogs studied (n=7) makes quantitative descriptions difficult.

Hexacarbons produce a neuropathy often described as central-peripheral distal axonopathy.[103] In cases of hexacarbon toxicity both ends of the first order neuron undergo toxic changes, such that pathology may be observed in the periphery and in the rostral extent of the dorsal columns. Since slowing of peripheral nerve conduction appears to precede clinical signs in n-hexane neurotoxicity,[104] recording SEPs from n-hexane exposed subjects should provide an even more sensitive indicator of neurotoxicity, requiring as it does conduction along both peripheral and central segments of the first order neuron.

Mutti et al.[105] recorded SEPs following median nerve stimulation in shoe factory workers with known occupational exposure (2-8 yrs) to hexane, cyclohexane, methyl-ethyl ketone and ethyl acetate. Recordings were made between 3 and 6 months after removal from exposure, so that all effects observed were considered chronic, and results were compared to an age-matched population of shoe factory workers with no known history

of exposure to these solvents. As expected, the exposed workers had significantly decreased conduction velocities in peripheral nerves. However there was only a slight increase in latency of peak N1 (N20) recorded from the scalp. The effect of exposure upon early components of the SEP appeared to be a disruption of the "W" response.[45] Much more impressive than the disrupted "W" response was the flattening of the later peaks (those occurring after 40 msec) in exposed subjects. The surprising feature of this study was the more robust detection of exposure by the peripheral nerve conduction velocity than by the SEP. The relative failure of the SEP in this study might reflect greater variability of measures of cerebral compared to peripheral activity, or might in some way reflect the late postexposure nature of the recordings. However the latter would seem on the surface to favor SEPs over peripheral nerve recordings.

In contrast to the Mutti et al.[105] study, Thomas et al.[106], who exposed baboons to 2,5-hexanedione, found increased SEP latencies and decreased peripheral nerve conduction velocities. Both measures were effective in detecting toxicity. These studies were done during the period of acute toxicity and under anesthesia. An interesting comparison was made between the effects of 2,5-hexanedione and the effects of clioquinol. Clioquinol, a halogenated hydroxyquinoline used as an antimicrobial agent, produces damage in the centrally-directed axons of dorsal root ganglion neurons, while sparing the peripherally-directed axons.[106] As expected, clioquinol produced little effect upon peripheral nerve conduction velocities. Peak P1 SEP latencies were significantly increased following stimulation of either the lower limb or the upper limb, but the magnitude of delay was substantially less than was

observed in the 2,5-hexanedione treated baboons. Unfortunately SEP amplitudes were not reported in this study, perhaps due to difficulties the authors indicated maintaining consistent levels of anesthesia. Both groups of treated animals exhibited similar clinical signs (lethargy, ataxia, paraparesis, hypotonia and piloerection), and neuropathological findings were consistent with expectations based upon previous studies. In this study, then, SEPs added little to the conduction velocity data in the 2,5-hexanedione case. In the case of clioquinol, the combined use of peripheral nerve conduction and SEP studies allowed an accurate assessment of the locus of damage.

Acrylamide is another neurotoxic substance which produces a central-peripheral axonopathy.[1)#] Boyes et al.[108] recorded SEPs produced by tibial nerve stimulation from rats exposed to acrylamide. The findings were surprising, because latency to N1, the second cortical peak in rats, was affected following fewer exposures than was latency to P1, the first cortical peak. Since any peripheral damage should have been reflected in a P1 latency shift, these data suggest that the central nervous system may be affected by acrylamide neurotoxicity more rapidly than the peripheral nervous system. Peaks beyond N1 were evidently unaffected. In a subsequent study using higher concentrations of acrylamide, Boyes and Cooper[109] recorded far-field SEPs from rats after 4, 8 and 16 days of exposure to 400 ppm acrylamide in drinking water. No changes were evident until the 16th day, at which point cumulative dose was about 600 mg/kg. On day 16 latencies of peaks II, III and P1 were significantly increased, while latency of peak I was not. Similarly, amplitude of peaks II, III and P1 were significantly decreased. The amplitude data are depicted in Fig 15. These findings also support the

interpretation that central damage occurs prior to peripheral damage, although it should be noted that the stimulation site was at the ankle, above the nerve terminals which should show the earliest peripheral damage. Therefore, the study was biased in favor of finding a CNS change first. In contrast to the findings of Perbellini et al.[104] with n-hexane, Boyes and Cooper[109] observed clinical signs of toxicity prior to electrophysiological signs of toxicity.

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insert Fig 15 about here

from Boyes and Cooper fig 2

More recently Arezzo et al.[110] performed a similar experiment in monkeys (Macaca fascicularis), injecting 10 mg/kg acrylamide subcutaneously 6 days/week. One monkey each was injected for 5, 15, 16, 50 and 83 days, and recordings were made once or twice a week. In this study, electrophysiological data recorded from the scalp were compared to (a) clinical signs of toxicity; (b) peripheral nerve conduction velocities; (c) evoked potentials recorded over the spinal cord; and (d) neuropathological findings. The results indicated clearly that conduction velocity and amplitude changes in the terminal and preterminal axons of the fasciculus gracilis preceded more peripherally occurring changes, and that these changes correlated well with the onset of neuropathological changes. The authors did not indicate whether more rostrally generated peaks were affected even earlier. In contrast to Boyes and Cooper[109], electrophysiological changes preceded clinical signs of toxicity.

In conclusion, SEPs and ffSEPs have been used only occasionally in studies of neurotoxicity. When dysfunction is diffuse, affecting more than one system, SEPs do not appear to have properties which recommend them more highly than evoked potential tests of other sensory systems. So few studies have employed SEPs in this context, that one must reserve final judgment on this issue. However when specific toxicity to the somatosensory system is suspected, SEPs may be useful in verifying toxicity and in pointing to the most sensitive links in the somatosensory chain. There is still disagreement regarding whether SEP changes may be observed prior to clinical signs of toxicity, but it seems reasonable to suppose that the resolution of this disagreement will depend upon the rigor of the respective clinical and electrophysiological examinations, the nature of the toxicant, the species and the number of subjects tested. It is not clear that resolution of the relative sensitivity of behavioral, physiological or other end-points has practical importance. It seems evident that all will continue to be useful, for all but the most rudimentary screening purposes, into the foreseeable future.

Performing SEP studies

To perform an adequate SEP study, many decisions must be made, including selection and preparation of the subjects, and details of the stimulation and recording situation. In most cases, the choices made will depend upon the nature of the questions posed by the investigator, and the preceding sections should be useful in helping the reader to make informed decisions. In the following sections, a few of the choice points will be identified.

Experimental Design

It is the nature of EP experiments in general that a multitude of endpoints are almost as easily acquired as a single endpoint. Thus, it is nearly as simple to measure all detectable peak amplitudes and latencies of a waveform as it is to measure only one. While this approach is essential for exploring one's data and designing future studies, it is rarely appreciated that including all of these variables in formal statistical analyses virtually assures (by chance) finding a "significant" effect. Detailed strategies for successfully dealing with this problem are outlined by Muller et al.[111]. An important take home message is that every effort should be made to (1) maximize the number of subjects tested; (2) minimize the number of dependent variables measured; and (3) minimize the number of independent variables manipulated. All of these measures will increase the power of statistical tests performed.

Not all studies are performed with the intent to make statements regarding the statistical probability of a particular effect. Many studies are intentionally qualitative, deal with only a few subjects, and may be best described as "demonstrations". For example, only a demonstration study is required to show that a particular waveform reverses polarity as the cortex is traversed. Demonstration type studies play a valuable role, but they should never be confused with statistically rigorous studies. Unfortunately the literature is replete with such confusion, because investigators who perform demonstration studies tend to pepper them with non-Bonferroni-corrected "t" tests, lending a superficial aura of statistical respect-

ability. Because toxicological studies with relevance to public health may be used in court cases, it is necessary that they be particularly rigorous, and caution is therefore recommended.

Selecting the Subject

As described previously, species, age, size and gender are all important determinants of SEP waveforms. While the decisions will depend upon the nature of the questions posed, it makes sense to think in terms of rodents for statistically controlled studies, because they are sufficiently economical to allow adequate sample sizes, and to think in terms of nonhuman primates for demonstration studies, because they are most like humans. Peculiarities of toxicant metabolism may conflict with the need to choose a cost-effective species although in most cases information on metabolism is not available.

Preparing the Subject

Once the subjects have been selected, the nature of subject preparation must be determined. Will the electrodes be chronic, or will they be placed at the time of recording? The former guarantees identical placement when multiple recordings are to be made, but also requires surgery with the attendent risks of infection. Will the subject be tested while anesthetized? Use of anesthesia, by relieving concerns about pain and movement artifacts, allows incorporation of higher stimulus intensities, thereby activating slower conducting axons. On the other hand, both anesthesia and intense stimulation are likely to produce results with questionable generality to the normal functioning organism. In some cases such generality may be more important than others. In toxicological studies one runs the risk of

using an anesthetic which interacts with the toxicant under study to produce a result which would not be observed in an unanesthetized subject.

Whether the subject is anesthetized or unanesthetized, care must be taken to ensure that temperature is controlled. Rectal temperature is not a good predictor of skin or nerve temperature, but when rectal temperature is not changing, it is a fairly good predictor of brain temperature. SEP studies must be concerned with both brain and nerve temperature, although neither have been given sufficient attention in the literature.

Decisions about Stimulating and Recording

The decisions required for most EP studies also apply here. One must decide upon a location for the active recording electrodes, a decision which may rest upon studies demonstrating the topographical distribution of the waveform on the surface of the brain. The topographical distribution of the waveform in turn depends upon the location of the stimulating electrode. Perhaps equally important is location of the reference electrode. As indicated above, a truly indifferent electrode is particularly difficult to find in ffSEP studies.

The characteristics of the recording amplifier (gain, coupling, and bandpass) depend upon the waveform as well. Studies of farfield responses require amplifiers with greater gain and a higher frequency response than do studies which focus upon later responses. Recommendations for bandpass settings are available from the literature, but care must be taken to ensure that the rolloff of the filters is understood before recommendations of others are applied routinely.[112,113]

The epoch length and the number of trials to average are often matters of personal preference, but the A/D conversion rate should exceed the highest frequency of the signal to be recognized by at least a factor of two.

Location of the stimulating electrodes, type of stimulating electrode, type of stimulus (mechanical vs electrical), stimulus intensity and stimulus rate all depend upon the specific questions the investigator intends to answer. In performing electrical stimulation studies, one does well to keep in mind some basic relationships between the stimulus properties and the properties of the tissue the stimulus is supposed to activate Ranck.[114]

Traditionally, analyses of SEPs have been performed upon peak latencies, onset latencies, peak to peak amplitudes and/or baseline to peak amplitudes. Interpeak latencies have been used to describe central conduction time, and an RMS measure of amplitude may be appropriate for a screening type exam. Other possibilities include spectral analysis of the waveform, and variability analysis.[115] However, it is worth worrying about data which are so highly derived that all intuitive explanatory value is lost.

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TABLE 1. Median nerve SEP Latency Coefficients of Variation (CVs) obtained in 7 Groups of Humans Reported by Giblin.[45]

	PEAK NAME			
	N20	N35	N55	N140
CV range	1-10%	2-14%	1-11%	2-12%
CV mean	5.57%	8.29%	7.4%	7.7%
CV SEMN	1.2	1.9	1.9	3.0
Number of studies reporting this peak	7	7	5	3

	P25	P30	P45	P80
CV range	0.2-17%	5-14%	1-16%	5-12%
CV mean	6.0%	9.75%	8.29%	8.25%
CV SEM	3.0	2.0	2.1	1.5
Number of studies reporting this peak	5	4	7	4

TABLE 2 Mean (±SD) Peak Latency of SEP Components in Man, Monkey, Cat and Rat[a]

	HUMAN (N=93)	MONKEY (N=5)	CAT (N=9)	RAT (N=6)
N10	10.1 (0.9)	5.3 (1.2)	2.8 (0.3)	1.5 (0.2)
N12a	11.6 (1.1)	5.9 (1.2)	3.6 (0.4)	1.7 (0.1)
N12b	12.2 (1.1)	6.4 (1.2)	4.2 (0.4)	2.5 (0.4)
N13a	13.5 (1.1)	7.5 (1.5)	5.4 (0.4)	3.0 (0.3)
N13b	13.8 (1.2)	8.0 (1.5)	5.8 (0.4)	3.4 (0.4)
N14	14.4 (1.1)	8.7 (1.6)	6.6 (0.5)	4.0 (0.5)
P15	15.1 (1.1)	9.3 (1.7)	7.7 (0.6)	4.9 (0.5)
P16	16.6 (1.1)	10.4 (1.8)	9.0 (0.5)	5.7 (0.5)
P18	18.3 (1.1)	11.3 (1.9)	10.2 (0.7)	6.6 (0.5)
N20/P20	19.2 (1.2)	12.0 (2.0)	11.3 (0.7)	7.5 (0.5)

[a]Data from Allison et al.[13]

TABLE 3. Recording Configurations for Rat SEPs in Fig 11

Reference Number	Fig 11 Section	Stim Locus	Rat Strain	Coordinates re: bregma (AP/Lat) Active	Reference	P1 Latency (msec)
63	A	Forepaw	S-D	+1,+2/3,4	Nasal Bone	7.23
87	B	Forepaw	S-D	+1/3.5	Post. Cortex	5.75
14	C	Forepaw	S-D	~+1/~4.5	~+16/0?	7.0
14	G	Hindpaw	S-D	~+1/~2.5	~+16/0?	~11.5
109	H	Hindpaw	S-D	0/2	~+30/0?	10.75
30	I	Hindleg	L-E	-2/2.5	-8/3	~50.
D	E	Tail	L-E	+2/2	-4/3	23.3
24	D	Tail	L-E	-2.5/2.5	+2/2	23.[b]
25	F	Tail	F-344	-2/2	Nasal Bone	27.5[c]

a Labelled P1, but probably P2
b Labelled P2, but probably P1
c Unlabelled, but probably P1
d Dyer, unpublished

FIGURE CAPTIONS

Figure 1. Schematic drawing of the major somatosensory pathways. A. Spinothalamic system; B. Dorsal column system. Circled numbers indicate the neuron number in the chain. Thus, 3 indicates third order neuron.

Figure 2. Mean and range of latencies for major peaks of SEPs recorded from the scalp of seven different groups of subjects. In all cases the contralateral median nerve was stimulated. The figure illustrates the extent of between study variability in SEPs. Data were obtained from Giblin.[45]

Figure 3. SEPs recorded from 4 epidural loci in the macaque brain following electrical stimulation of the contralateral median nerve. Arrows mark the stimulus onset. Peaks are identified by polarity (P vs N) and latency. The SEPs recorded from different loci vary in amplitude, relative prominence of peaks, and in some cases polarity of peaks. Redrawn from Arezzo et al.[7]

Figure 4. Isopotential maps illustrating, from the surface distribution for several of the peaks identified in Fig. 3, that not all of the peaks in the macaque median nerve evoked SEP are generated in the same cortical area. Areas where the amplitude recorded was greater than 90% of the maximum amplitude are darkened. Each outer line reflects progressive 10% reductions in amplitude. Redrawn from Arezzo et al.[7]

Figure 5. SEPs recorded from different depths within the cortex of macaques at two cortical sites, A and B. Distances listed adjacent to recordings indicate the depth from the cortical surface. Note the polarity reversal, particularly evident for the initial deflection. Redrawn from Arezzo et al.[7]

Figure 6. Averaged SEPs recorded in a human following 1000 stimulations of the median nerve at the wrist. Simultaneous recordings from the contralateral central area (C_4) and two neck regions (C2, C7), all referred to the midforehead (f_{pz}). Redrawn from Hume and Cant.[6]

Figure 7. A. Scheme showing relative latencies of human and animal early SEP components. For comparison, the peaks corresponding to the human N10 and N20/P20 are aligned with the human peaks, and other components in the animals are drawn proportionally. Each waveform is a composite of features recorded from different loci. B. Scheme illustrating one view, based on recording from animals, of the primary generators of each component. Redrawn from Allison et al.[13]

Figure 8. Simple example illustrating how the presence of gyri can distort potentials recorded from the surface. A. The undistorted case. B. Potential inversion produced by the presence of gyri.

Figure 9. Composite map illustrating the cutaneous representation in the primary somatosensory cortex of the anesthetized rat, determined by microelectrode mapping. Abbreviations: T, trunk; hl, hindlimb; HP, hindpaw; dhp, dorsal hindpaw; dl-5, digits 1-5 of hindpaw; hm, hindlimb muscle; vfl, ventral forelimb; dfl, dorsal forelimb; w, wrist whiskers; dfp, dorsal forepaw; p, palm; d2-5, digits 2-5 of forepaw; t, thumb; UZ, unresponsive

zone; A-E, 1-8, rows (from dorsal to ventral) and numbers (from caudal to rostral) of mystacial vibrissae; RV rostral small vibrissae; N, nose; FBP, frontobuccal pads; UL, upper lip; LL, lower lip; LJ, lower jaw; SII, secondary somatosensory cortex. Redrawn from Chapin and Lin.[26]

Figure 10. Map of somatosensory cortex in the rat in proportion to the cerebral hemisphere, and based upon single or multiple unit responses to light tactile stimuli recorded from 16 rats. FL, foreleg; HL, hindleg; T, truck; H, head. Redrawn from Hall and Lindholm.[27]

Figure 11. Composite figure showing SEPs recorded for rats from various loci. Details are indicated in Table 3.

Figure 12. Pooled data on N1 duration and N1 onset latency in humans, as a function of age and body size. A, N1 duration in msec, with curve drawn according to a calculated power function. B, N1 onset latency in msec. C, ascending function, change in body size with age; descending function, onset latency divided by body length in msec/m, with curve drawn according to a calculated power function. Redrawn from Desmedt et al.[35]

Figure 13. SEPs recorded from cats, showing the effect of increasing stimulus intensity beyond twitch threshold. A. Effects of stimulus intensity (stimuli presented at posterior tibial nerve). B. One cat's SEP at 20X motor threshold. Values shown in the table are mean peak latencies and standard deviations based upon 14 cats. Redrawn from Powers et al.[53]

Figure 14. Mean (SEM) Peak-to-peak amplitude of N1P1(N18-P22) of the SEP recorded from C4 among subjects with different maximal blood lead levels. Redrawn from Seppalainen.[100]

Figure 15. Mean (± SEM) far field SEP amplitudes recorded from rats given either, unlimited access to water, paired water, or 400 ppm and acrylamide in water daily for 16 days. Redrawn from Boyes and Cooper.[109]

Dyer - 70

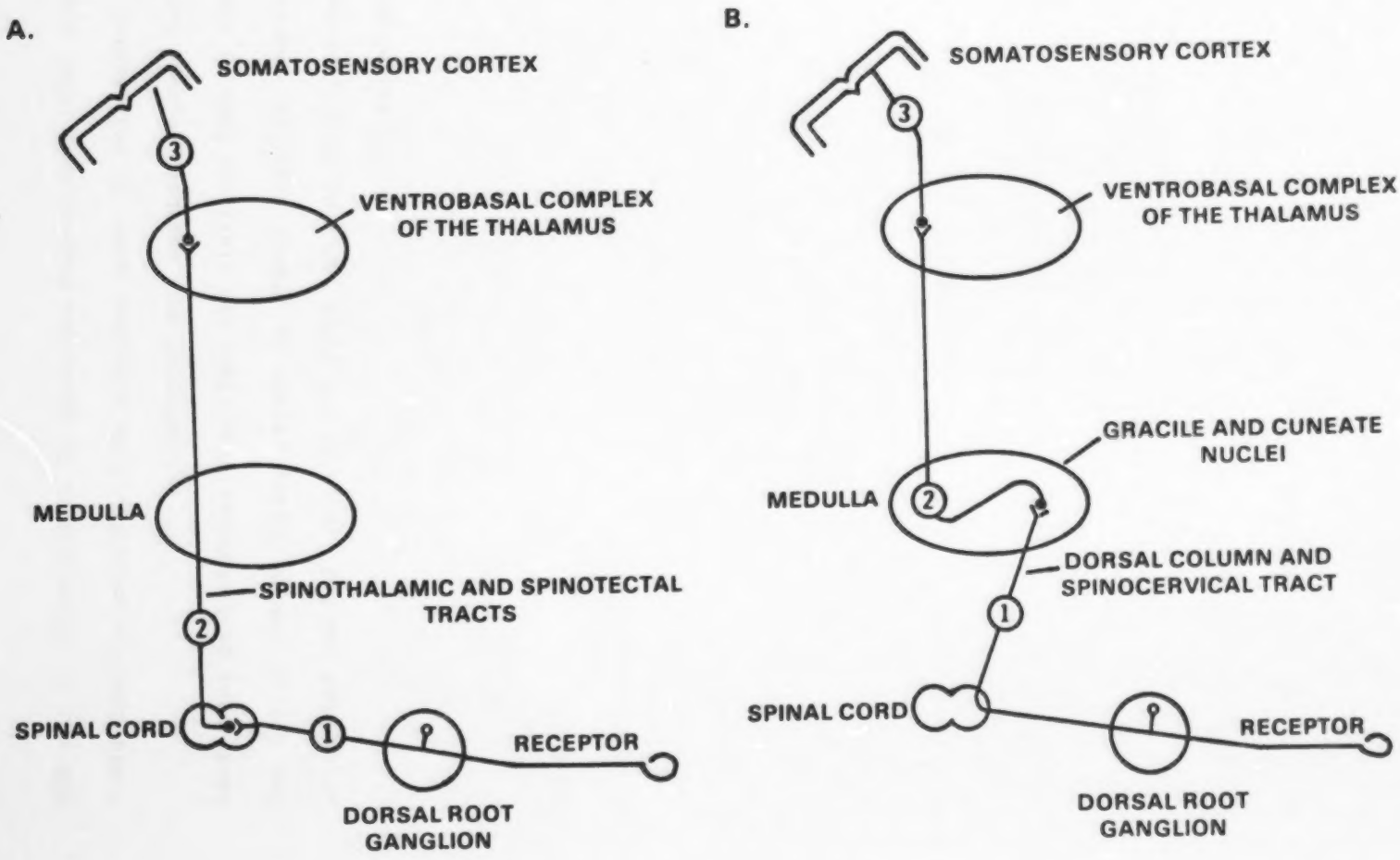

A.
SOMATOSENSORY CORTEX
3
VENTROBASAL COMPLEX OF THE THALAMUS
MEDULLA
SPINOTHALAMIC AND SPINOTECTAL TRACTS
2
SPINAL CORD
1
RECEPTOR
DORSAL ROOT GANGLION
B.
SOMATOSENSORY CORTEX
3
VENTROBASAL COMPLEX OF THE THALAMUS
GRACILE AND CUNEATE NUCLEI
MEDULLA
2
DORSAL COLUMN AND SPINOCERVICAL TRACT
1
SPINAL CORD
RECEPTOR
DORSAL ROOT GANGLION

Fig 1

Dyer-71

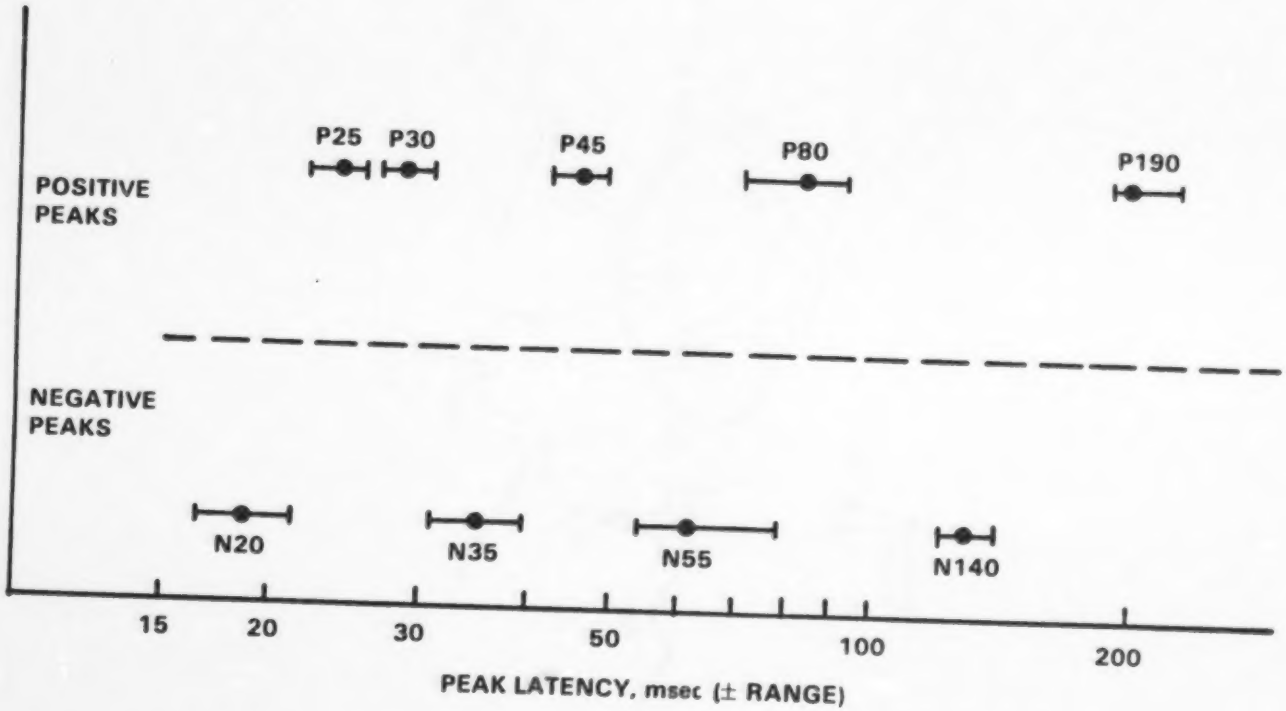

POSITIVE PEAKS
P25
P30
P45
P80
P190
NEGATIVE PEAKS
N20
N35
N55
N140
15
20
30
50
100
200
PEAK LATENCY, msec (± RANGE)

Fig 2

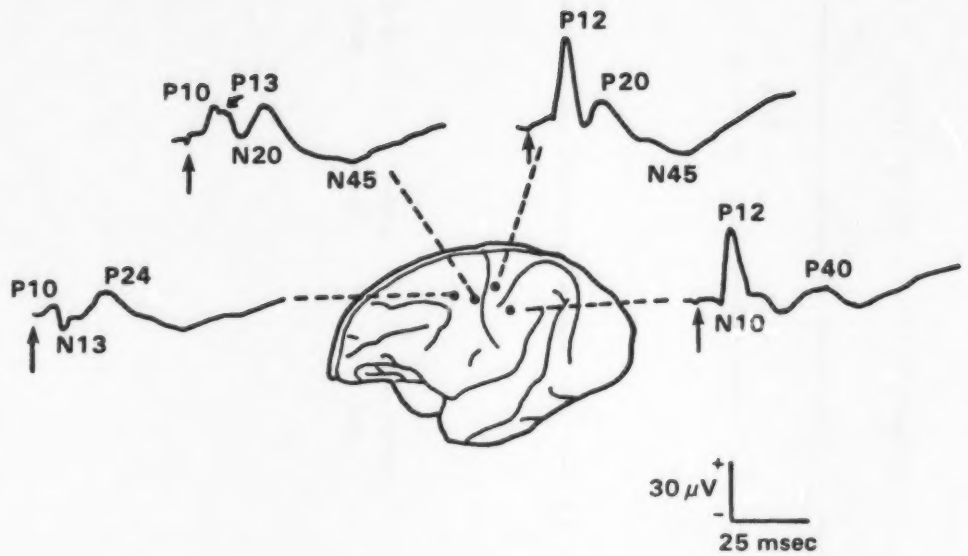


FIG 3

DYER '73

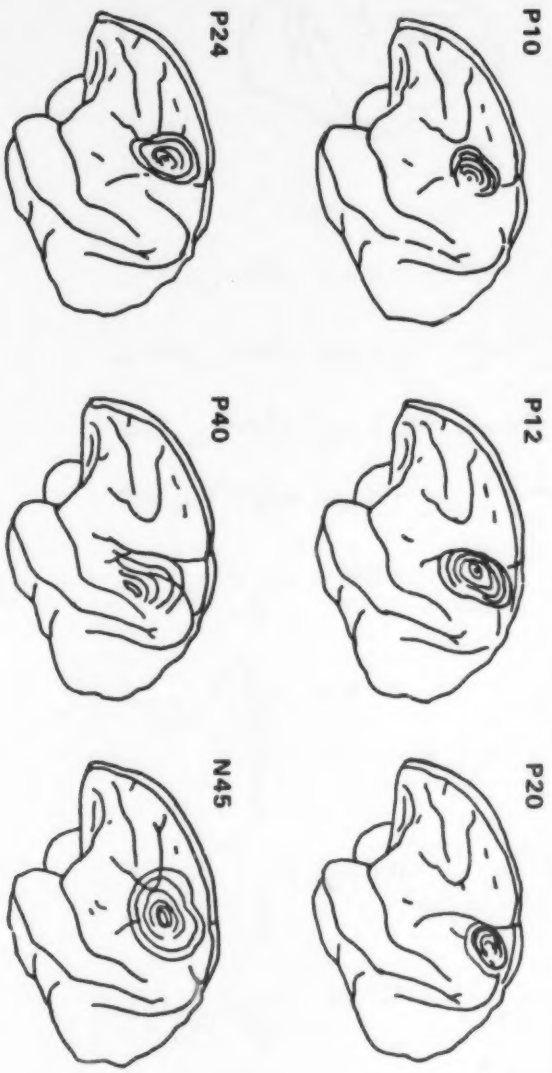


FIG 4

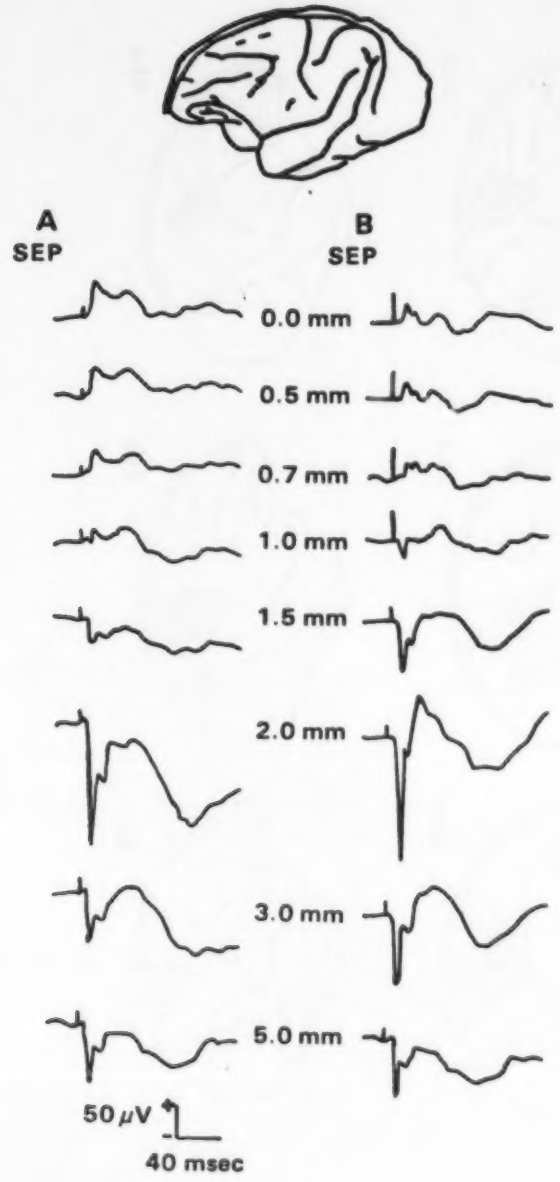

A
SEP
B
SEP
0.0 mm
0.5 mm
0.7 mm
1.0 mm
1.5 mm
2.0 mm
3.0 mm
5.0 mm
50 μV
40 msec

FIG 5

DYER- 75

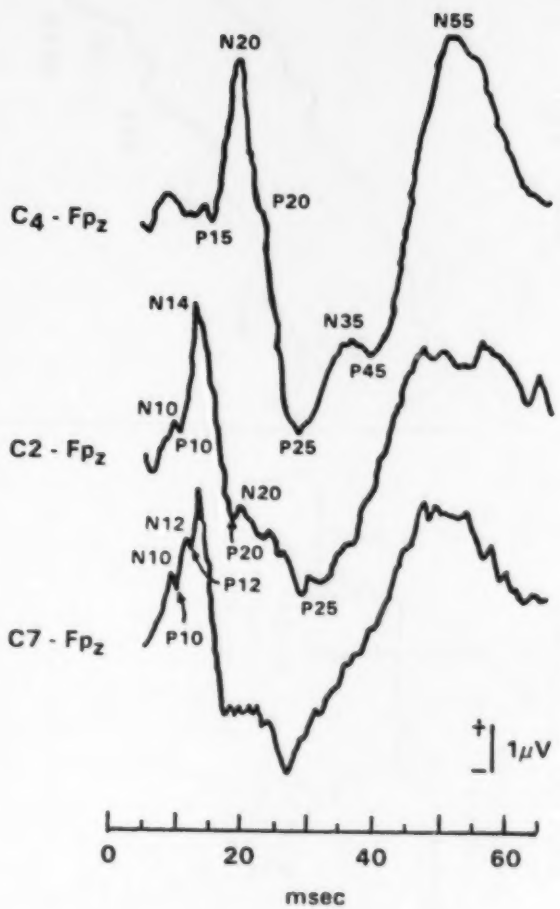

N20
N55
C4 - Fpz
P15
P20
N14
N35
P45
N10
P10
C2 - Fpz
P25
N20
N12
N10
P20
P12
P25
C7 - Fpz
P10
+
−
1μV
0
20
40
60
msec

Fig 6

Dyer-'76

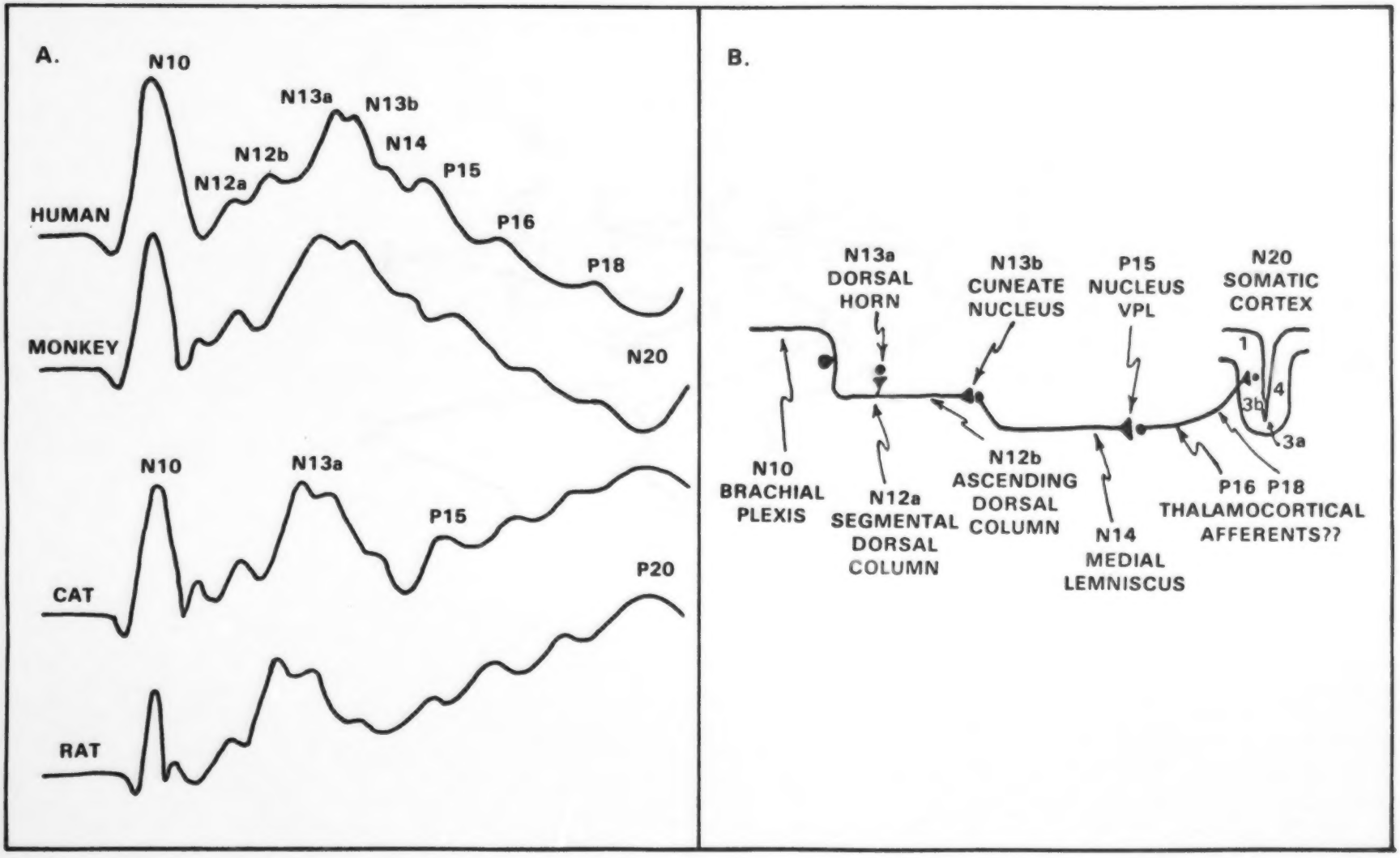

A.
N10
N13a
N13b
N12b
N14
N12a
P15
HUMAN
P16
P18
MONKEY
N20
N10
N13a
P15
CAT
P20
RAT
B.
N13a
DORSAL
HORN
N13b
CUNEATE
NUCLEUS
P15
NUCLEUS
VPL
N20
SOMATIC
CORTEX
1
4
3b
3a
N10
BRACHIAL
PLEXIS
N12a
SEGMENTAL
DORSAL
COLUMN
N12b
ASCENDING
DORSAL
COLUMN
N14
MEDIAL
LEMNISCUS
P16 P18
THALAMOCORTICAL
AFFERENTS??

Fig 7

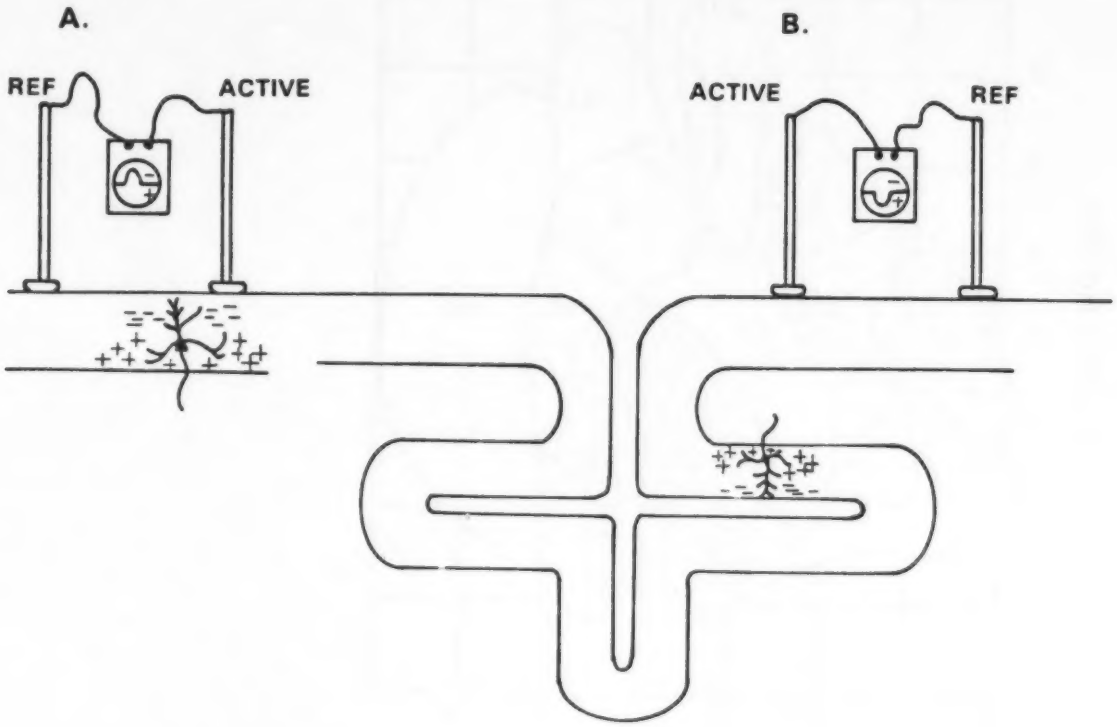


FIG 8

DYER-78

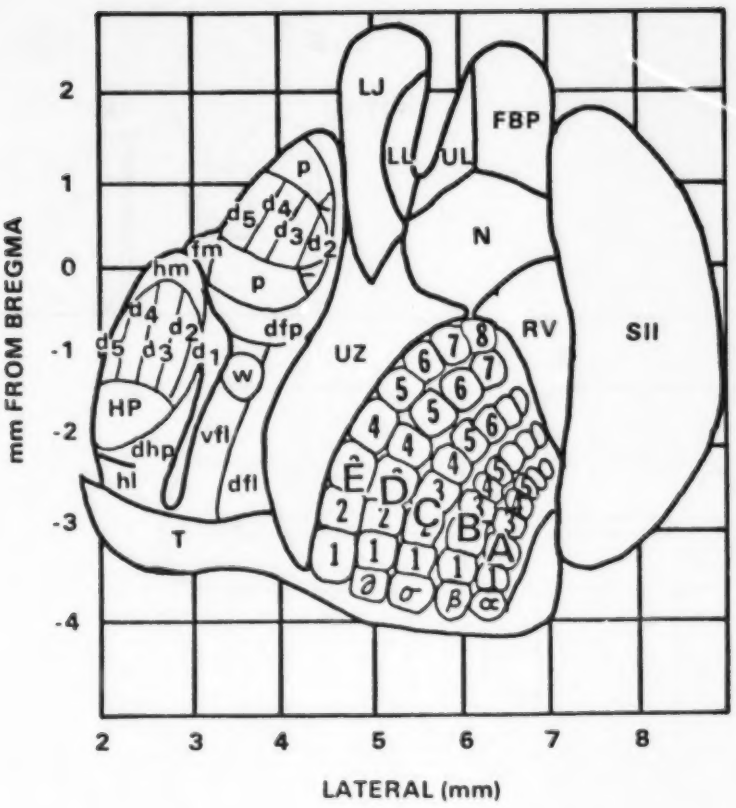

mm FROM BREGMA
2
1
0
-1
-2
-3
-4
2
3
4
5
6
7
8
LATERAL (mm)
LJ
FBP
LL
UL
N
RV
SII
UZ
p
d5
d4
d3
d2
fm
hm
p
dfp
d5
d4
d3
d2
d1
w
HP
dhp
vfl
hl
dfl
T
Ê
D̂
Ç
B̂
A
∂
σ
β
α

FIG 9

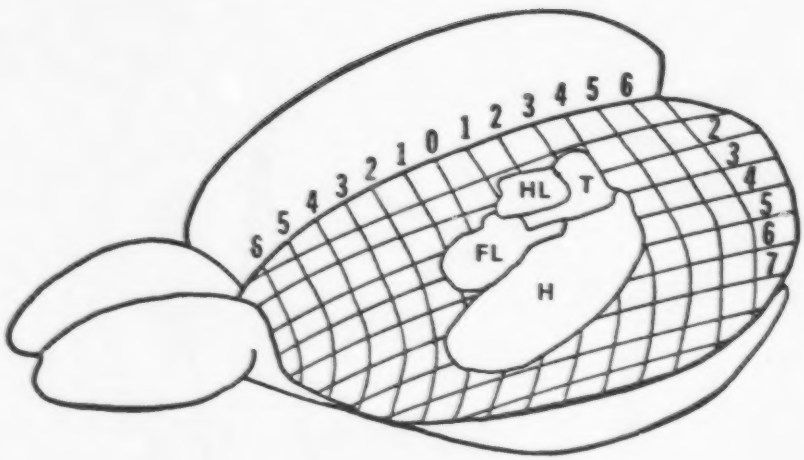


Fig 10'

Dyer-80

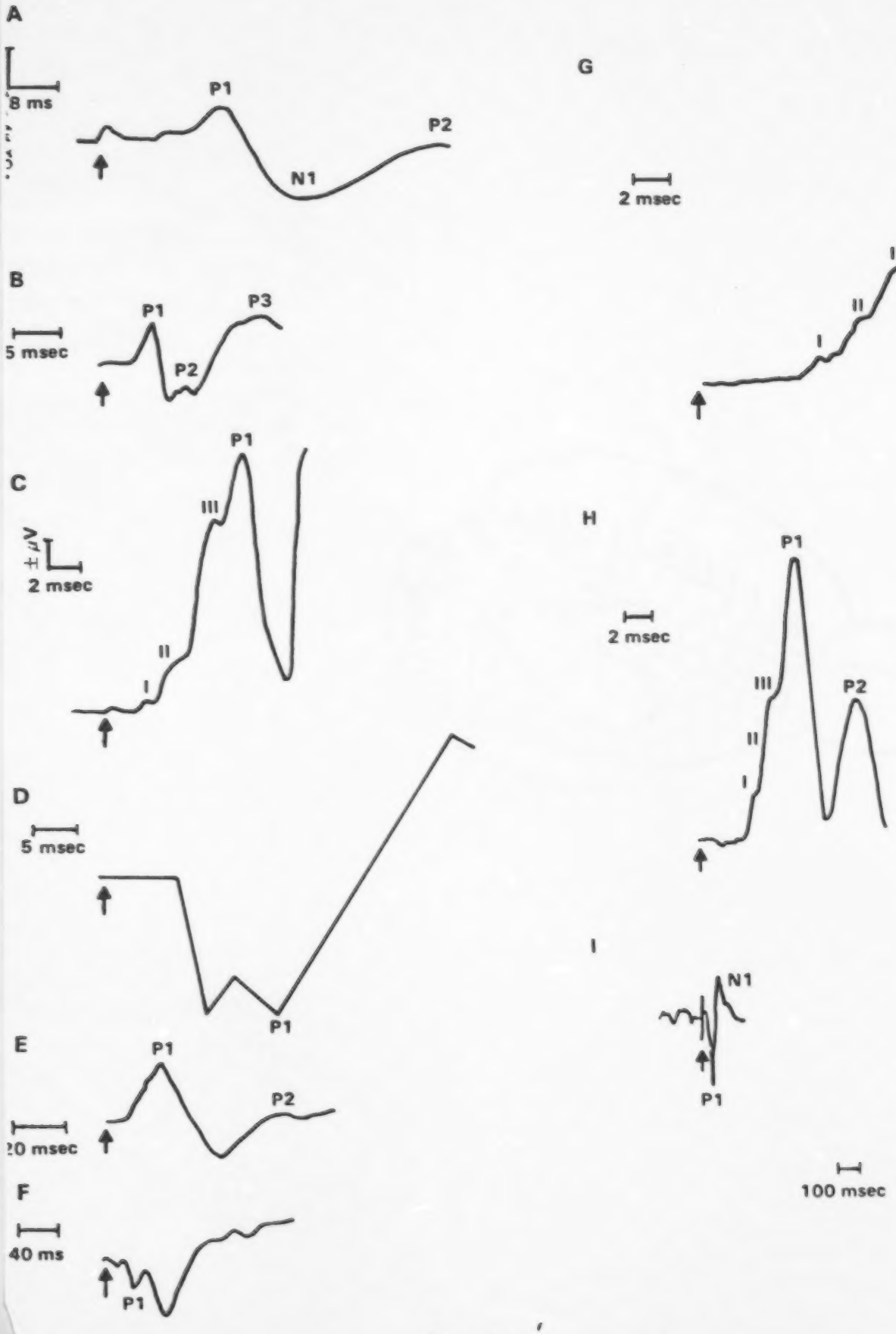
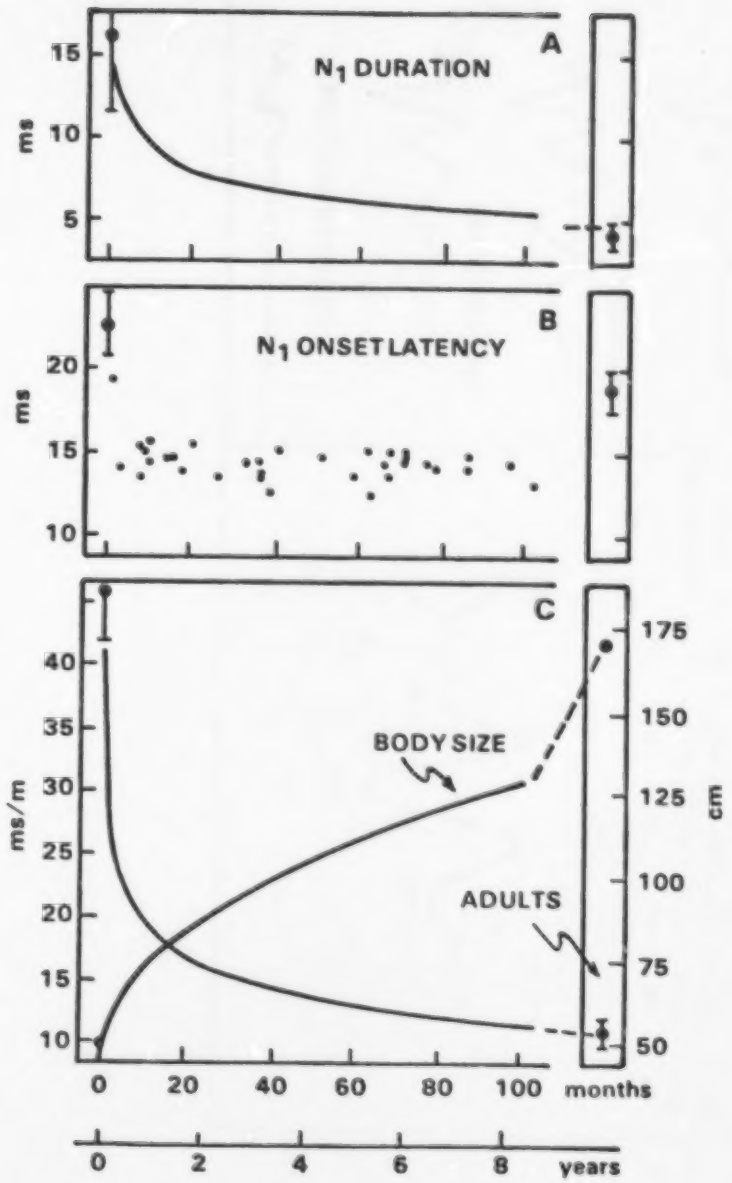
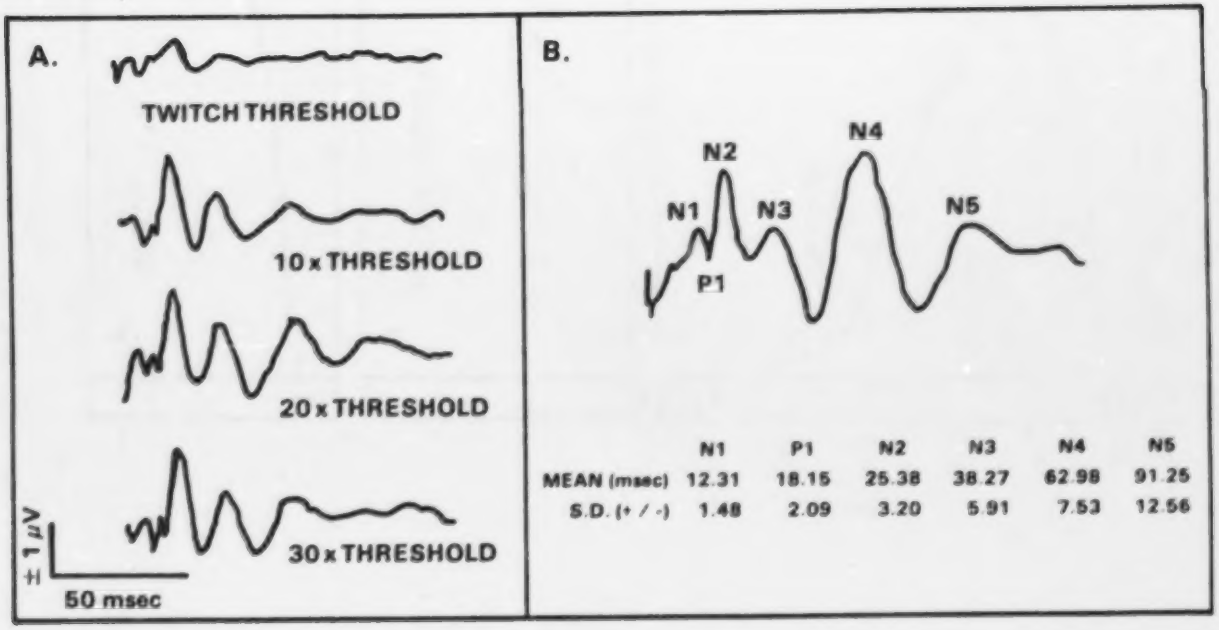


Fig 11


A
N_1 DURATION
ms
15
10
5
B
N_1 ONSET LATENCY
ms
20
15
10
C
ms/m
40
35
30
25
20
15
10
BODY SIZE
ADULTS
cm
175
150
125
100
75
50
0
20
40
60
80
100
months
0
2
4
6
8
years

F1612

DYER-82



	N1	P1	N2	N3	N4	N5
MEAN (msec)	12.31	18.15	25.38	38.27	62.98	91.25
S.D. (+ / -)	1.48	2.09	3.20	5.91	7.53	12.56

FIG 13

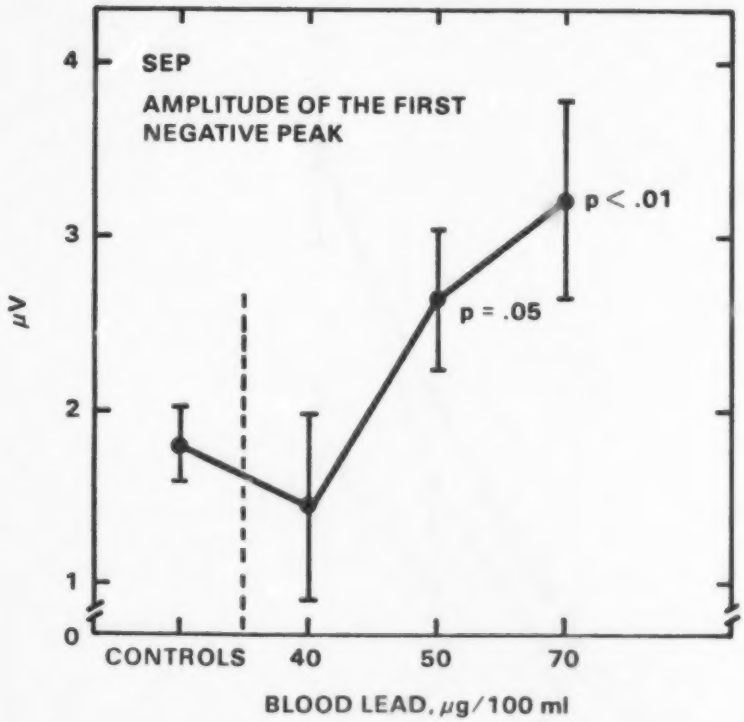

SEP
AMPLITUDE OF THE FIRST NEGATIVE PEAK
p < .01
p = .05
μV
4
3
2
1
0
CONTROLS
40
50
70
BLOOD LEAD, μg/100 ml

FIG 14

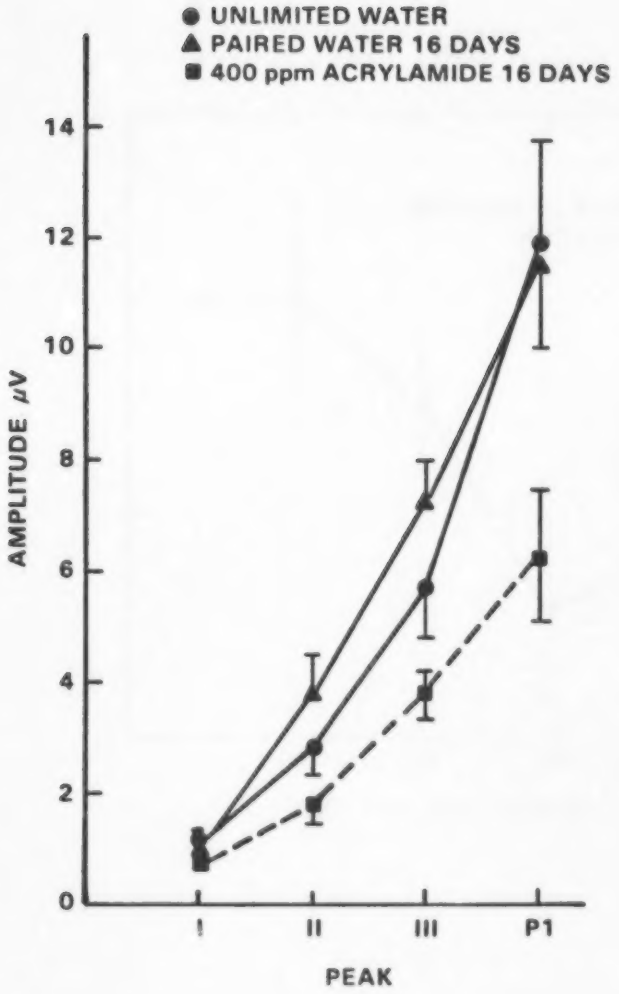

UNLIMITED WATER
PAIRED WATER 16 DAYS
400 ppm ACRYLAMIDE 16 DAYS
AMPLITUDE μV
0
2
4
6
8
10
12
14
I
II
III
P1
PEAK

FIG 15